

CLINICAL DIAGNOSIS OF CARPAL TUNNEL SYNDROME

**CLINICAL DIAGNOSIS OF CARPAL TUNNEL SYNDROME: A SYSTEMATIC
REVIEW AND COGNITIVE INTERVIEWING STUDY OF A DIAGNOSTIC
QUESTIONNAIRE**

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements
for the Degree Master of Science in Rehabilitation Sciences

M.Sc. Thesis – A. Dabbagh; McMaster University – Rehabilitation Science

MASTER OF SCIENCE (2019) in Rehabilitation Science

McMaster University, Hamilton, Ontario, Canada

TITLE: Clinical diagnosis of Carpal Tunnel Syndrome: A Systematic Review and Cognitive Interviewing study of a Diagnostic Questionnaire

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NUMBER OF PAGES: xvi, 140

Thesis Lay Abstract

Carpal tunnel syndrome is a condition affecting the hands, causing feelings of burning pain, pins and needles, heaviness and/or lack of sensation. This condition is very common among people who do manual work and can make them unable to do their jobs and daily living tasks. Early diagnosis of carpal tunnel syndrome is very important in starting an appropriate plan of treatment. The best diagnostic test for carpal tunnel syndrome is still uncertain.

In the first study, we collected studies of the questionnaires and hand maps that exist for the diagnosis of carpal tunnel syndrome. We then tried to summarize the information that assists clinicians in making a diagnostic decision. In the second study, we interviewed people about their opinion of a questionnaire that is used in hand clinics to diagnose carpal tunnel syndrome.

We concluded that more studies with high quality are needed to confidently decide which diagnostic test is best. Also, we revised a questionnaire that is currently used, and we hope that these revisions make the questionnaire more detailed and understandable for people.

Thesis Abstract

Background: Carpal Tunnel Syndrome (CTS) is a condition affecting wrists and hands, causing pain, tingling, and numbness. Despite the high prevalence of CTS and the existence of several diagnostic tools, there is no consensus over a diagnostic gold standard test.

Thesis Objectives: To conduct a systematic review of diagnostic test accuracy of clinical scales, questionnaires and hand symptom diagrams/maps for the diagnosis of CTS in people suspected with this condition; and to do a cognitive interviewing qualitative study of the Kamath and Stothard questionnaire, a diagnostic tool for CTS, to identify and resolve potential sources of error.

Methods: In the first study, we searched MEDLINE, CINAHL, and Embase databases keywords related to diagnostic accuracy and clinical tests of CTS. In the second study, we interviewed clinicians and people diagnosed with CTS and other upper extremity conditions. We recorded, and content analyzed their opinion on comprehensiveness and comprehensibility of Kamath and Stothard questionnaire.

Results: Twenty-one articles met the eligibility criteria of the systematic review, of which nine were on the diagnostic accuracy of hand symptom diagrams and twelve assessed the diagnostic accuracy of clinical scales and questionnaires for the diagnosis of CTS. Positive likelihood ratios (LRs) to diagnose or rule in CTS ranged from 0.94 for Boston carpal tunnel questionnaire to 10.5 for CTS-6 scale, and negative LRs to rule out CTS ranged from 1.05 to 0.05 for the same diagnostic tools. In the cognitive interviewing study, we categorized the areas of uncertainty in the participants' responses into five themes: clarity and comprehension (51%),

relativeness (38%), inadequate response definition (3.75%), perspective modifiers (3.75%), and reference point (2.5%).

Conclusions: Very few high-quality studies exist on the diagnostic accuracy of CTS-6, Kamath and Stothard questionnaire, Bland questionnaire, and Katz and Stirrat's hand symptom diagram. By doing cognitive interviews, we identified options for potential improvement in the wording of the Kamath and Stothard questionnaire. Future studies should assess the diagnostic properties of the proposed modified questionnaire, and high-quality studies are warranted to assist in deciding on ruling in or out CTS.

Acknowledgements

First, I would like to express my life long gratitude towards my amazing supervisor, Dr. Joy MacDermid, who is more than an academic supervisor to me. She changed my life forever and showed me a way to life, I had never imagined before; my supervisory committee, Dr. Luciana Macedo and Dr. Tara Packham, were the most wonderful professors I could have ever asked for, they always helped me when I needed their assistance. Thank you all for your continuous support and guidance throughout my master's study and related research, thank you for your patience, motivation, and immense support.

I would also like to thank the participants who were involved in the cognitive interviews for this research project. Without their passionate participation and input, this study could not have been successfully conducted.

I would like to thank Margaret Lomotan at McMaster University for her continuous support throughout my education. Also, Joshua Yong, for accepting to be my second reviewer.

Mom and dad, you always supported and pushed me to be a better person in life. To desire more, to think broader, and to struggle and push myself to achieve my dreams. I'd like to express my deepest thanks and love to you and my entire family, to Babak, my aunts, my cousins, and my close friends, without your support, none of this could become possible.

Thanks to my peer students at McMaster University, with you I experienced a healthy and lovely and productive academic environment. Thanks to Joshua, Janelle, Mike, Shannon, Monika, Kinely, Natalie, Maysa, Linda, Rachel, Shereen, Heather and many more.

Table of Contents

Thesis Lay Abstract	iv
Thesis Abstract.....	v
Acknowledgements.....	viii
List of Abbreviations	xv
Declaration of Academic Achievement	xvi

<i>Chapter One: Introduction to Etiology, Epidemiology, Risk Factors, Management, and Diagnosis of Carpal Tunnel Syndrome.....</i>	<i>1</i>
1.1 Etiology/description of carpal tunnel syndrome	2
1.2 CTS Risk Factors	3
1.3 CTS Epidemiology and Burden	4
1.4 CTS Management	5
1.5 CTS Diagnosis	6
1.4.1 Electrodiagnosis.....	7
1.5.2 Magnetic Resonance Imaging.....	8
1.5.3 Diagnostic Ultrasonography	8
1.5.4 Clinical tests.....	9
1.6 Kamath and Stothard Questionnaire	11
1.7 Analytical Approach Central to the Thesis.....	14
1.8 Current Gaps in the Literature regarding CTS Diagnosis.....	15
1.9 Thesis Objectives and Composition of Papers.....	17
1.10 References.....	19

Chapter Two: Diagnostic Accuracy of Scales, Questionnaires and Hand Symptom

Diagrams for the Diagnosis of Carpal Tunnel Syndrome: A Systematic Review of Diagnostic

<i>Test Accuracy</i>	28
2.0 Abstract	30
2.1 BACKGROUND	32
2.2 METHODS	33
2.2.1 Information Sources	34
2.2.2 Study Selection	34
2.2.3 Eligibility Criteria	35
2.2.4 Data Extraction	36
2.2.5 Data synthesis and analysis.....	37
2.2.6 Assessment of risk of bias.....	38
2.3 RESULTS	39
2.3.1 Selection of Studies and Methodological Assessment.....	39
2.3.2 Diagnostic Accuracy of the diagnostic Scales and Questionnaires for CTS diagnosis	41
2.3.3 Diagnostic Accuracy of Hand diagrams/maps for CTS diagnosis.....	44
2.3.4 Reference standards for CTS diagnosis	45
2.4 DISCUSSION	45
2.4.1 Scales and questionnaires to diagnose CTS.....	46
2.4.2 Hand symptoms diagrams/maps to diagnose CTS.....	48
2.4.3 Limitations	50

2.5 CONCLUSION.....	50
2.6 References.....	64
2.7 Appendices.....	68
<i>Chapter Three: Content validation of the Kamath and Stothard questionnaire: a cognitive interviewing study.....</i>	78
3.0 Abstract:	80
3.1 Introduction.....	82
3.1.1 Purpose of the study.....	83
3.2 Methods.....	83
3.2.1 Study design and ethics.....	83
3.2.2 Sampling and participants.....	84
3.2.3 Recruitment.....	84
3.2.4 Inclusion and exclusion criteria	85
3.2.5 Demographic data	86
3.2.6 Cognitive interviewing procedure.....	86
3.2.7 Sample size and saturation.....	87
3.2.8 Data analysis	88
3.3 Findings.....	88
3.3.1 Participants.....	88
3.3.2 Problematic themes identified by cognitive interviewing	89
3.3.3 Participants’ opinion on content coverage.....	95
3.4 Discussion.....	95

3.4.1 Recommendations on potential addition of questions to the Kamath and Stothard questionnaire	100
3.4.2 Limitations	104
3.5 Conclusion	104
3.6 References.....	105
2.7 Appendices.....	109
Chapter Four: Concluding Remarks and Future Directions	121
4.1. Overview of thesis manuscripts and their linkage	122
4.2 Lay summaries of thesis manuscripts	124
4.2.1 Lay summary of the first study: Diagnostic Accuracy of Scales, Questionnaires and Hand Symptom Diagrams for the Diagnosis of Carpal Tunnel Syndrome: A Systematic Review of Diagnostic Test Accuracy	124
4.2.2 Lay summary of the second study: Content validation of the Kamath and Stothard questionnaire: a cognitive interviewing study.....	125
4.3 List of Key Findings	126
4.4 Limitations	127
4.5 Impact of research and practice implications.....	129
4.6 Knowledge Translation Recommendations	130
4.7 Future Research Directions.....	131
4.8 Dissemination Plans.....	131
4.9 References.....	132

List of Tables

Table 2.1 Description of Scales, Questionnaires and Hand Symptom Diagrams for Carpal Tunnel Syndrome.....	42
Table 2.2 Characteristics of the studies assessing diagnostic Scales and Questionnaires for the diagnosis of CTS and the reference standards in each individual study	51
Table 2.3 Characteristics of the studies assessing symptom diagrams/maps for the diagnosis of CTS and their reference standards in each individual study	57
Table 2.4 Diagnostic Accuracy of Scales and Questionnaires for CTS diagnosis	62
Table 2.5 Diagnostic Accuracy of the Symptom Diagrams/Maps for CTS diagnosis	63
Table 3.1 Participants Demographic information.....	89
Table 3.4 Suggested modified questionnaire	102
Table 3.2 Cross-item analysis summary of the response errors.....	107
Table 3.3 Modified versus original questions on Kamath and Stothard Questionnaire .	108

List of Figures

Figure 2.1 PRISMA flow diagram.....	40
Figure 2.2 The proportion of included studies with low, high, or unclear risk of bias and concerns regarding the applicability, using QUADAS-2 tool	41
Figure 2.3 Risk of bias and applicability concerns of the included studies	44
Figure 3.2 Katz and Stirrat's hand diagram ²⁰	103

List of Appendices

Appendix 2.A: Search strategies in Medline, CINAHL, and Embase..... 68

Appendix 2.B Conflicts of interest for included studies..... 77

Appendix 3.A KAMATH and STOTHARD Questionnaire¹ 109

Appendix 3.C Information letter/consent forms 110

Appendix 3.D Recruitment e-mail..... 114

Appendix 3.E Recruitment flyer 115

Appendix 3.F Recruitment poster 116

Appendix 3.G Pre-planned probes 117

List of Abbreviations

CTS	Carpal Tunnel Syndrome
SR	Systematic Review
HSD	Hand Symptom Diagram
CI	Cognitive Interview
NCS	Nerve Conduction Studies
EDX	Electrodiagnosis
SD	Standard Deviation
95% CI	95% Confidence Interval
HiREB	Hamilton Integrated Research Ethics Board
AANEM	American Association of Neuromuscular and Electrodiagnostic Medicine
MRI	Magnetic Resonance Imaging
PROSPERO	International database of prospectively registered systematic reviews
UE	Upper Extremity

Declaration of Academic Achievement

Armaghan Dabbagh is the primary author and contributor of this thesis. She was responsible for completing an ethics approval on the HiREB, registering the systematic review study on PROSPERO, recruiting participants, providing informed consent, conduction of the interviews, data extraction, analysis, and interpretation. She was also responsible for drafting of the manuscripts and incorporating feedback. Dr. Joy C. MacDermid was the thesis supervisor and funder, who was responsible for reviewing and refining the research questions, study design and manuscripts. The supervisory committee, Dr. Luciana G. Macedo, and Dr. Tara L. Packham, provided guidance and feedback during the committee meetings and reviewed the manuscripts. They both helped in the recruitment of the participants for this thesis, by sending emails to potentially interested clinicians, and sharing the flyers.

**Chapter One: Introduction to Etiology, Epidemiology, Risk Factors,
Management, and Diagnosis of Carpal Tunnel Syndrome**

1.1 Etiology/description of carpal tunnel syndrome

The carpal tunnel is an osteofibrous outlet surrounded by the flexor retinaculum and the carpal bones (Aboonq, 2015). The transverse carpal ligament forms the roof of this canal in which the median nerve and nine flexor tendons are located (Aboonq, 2015). Carpal Tunnel Syndrome (CTS) happens as a result of increased pressure in the canal and entrapment of the median nerve at the level of the wrist. From a pathophysiological viewpoint, compressive neuropathies develop due to the compression and tension of the nerves.

There are two locations in the carpal canal where the median nerve can be compressed: 1) the proximal part of the canal, where prolonged wrist flexion can cause thickness and stiffness of the forearm fascia and flexor retinaculum; 2) at the narrowest part of the carpal canal, close to the hook of hamate (Duncan & Kakinoki, 2017). After passing through the carpal canal, the median nerve bifurcates into recurrent and palmar digital cutaneous branches (Duncan & Kakinoki, 2017). These branches then innervate the palmar surface of the lateral three and a half digits, the thenar muscles and the first two lumbrical muscles (Duncan & Kakinoki, 2017).

Sign and symptoms of CTS are initially limited to sensory deficits of the median nerve cutaneous distribution, e.g. tingling, numbness and pain that occur at night (Chammas et al., 2014). A tendency to keep the wrist in a prolonged flexion position, lack of a muscle pump to help in the drainage of the interstitial fluids, and an increased arterial pressure at nights, are factors that contribute to the nocturnal signs and symptoms of CTS in the early stages (Chammas et al., 2014). These sign and symptoms can then progress into diurnal and nocturnal in combination with weakness and atrophy of the thenar muscles (Chammas et al., 2014). At this stage destruction of median nerve begins to occurs at the myelin sheath and nodes of Ranvier (Chammas et al., 2014).

Functional signs and symptoms of CTS also include weakness of grip strength, dropping small items and loss of dexterity and decreased ability to do fine movements (Chammas et al., 2014).

Before CTS was introduced for the first time by Paget in 1854 (Aboonq, 2015), CTS related symptoms were often attributed to other aetiologies, such as brachial plexus compression and thenar neuritis (Duncan & Kakinoki, 2017). According to Chammas, the etiology of CTS can be divided into idiopathic and secondary CTS (Chammas et al., 2014). Most of the CTS cases are idiopathic, meaning that they don't have any specific cause (Chammas et al., 2014). Secondary CTS cases happen as a result of excessive flexion and extension movements of the wrist and the hypertrophy of the flexor tendons synovial sheaths (Aboonq, 2015).

1.2 CTS Risk Factors

Although several risk factors have been identified that contribute to the onset of CTS, the true mechanism of 'injury' is still unknown. According to the 2016 guidelines of the American Association of Orthopedic Surgeons (AAOS) on CTS treatment, strong evidence has been identified on the association of high BMI and hand/wrist repetitive manual tasks with the occurrence of CTS (American Academy of Orthopaedic Surgeons, 2016). In a recent systematic review and meta-analysis of the association of obesity and gender with the risk of carpal tunnel syndrome, 58 studies were explored (Shiri, Pourmemari, Falah-Hassani, & Viikari-Juntura, 2015). They identified a two-fold increase in the risk of CTS for obese people, regardless of their gender (Shiri et al., 2015). Other risk factors suggested to also contribute to the development of CTS

include wrist ratio/index, rheumatoid arthritis, psychosocial factors, distal upper extremity tendinopathies, gardening, assembly line work, computer work, exposure to vibration, and workplace demands for forceful grip (American Academy of Orthopaedic Surgeons, 2016).

1.3 CTS Epidemiology and Burden

CTS is the most common peripheral mononeuropathy of the upper extremity, accounting for almost 90% of all entrapment neuropathies. This condition roughly affects 4-5% of the population (Atroshi et al., 1999). The prevalence of idiopathic CTS is higher among middle-aged women between 40 and 60 years old (9.2%) compared to the men (6%) (Meems, Truijens, Spek, Visser, & Pop, 2015). 50 to 60% of the CTS cases are bilateral (Meems et al., 2015), and the frequency of bilateral CTS increases with the duration of symptoms (Falkiner & Myers, 2002). In high-risk occupational groups such as ‘skilled trades’ and ‘administrative and secretarial’ the incidence is very high and reaches to 136 (95% CI 115–158) and 82 (95% CI 64–99) per 100,000 working people annually (Squissato & Brown, 2014).

The economic burden associated with CTS has been estimated to be around \$45,000–\$89,000 per claimant in the USA in the period from 1990 to 2001 (Foley, Silverstein, & Polissar, 2007). In the study by Foley et al., the earning records of 4,443 workers in Washington who filed claims for CTS were compared to 2,544 claims for upper-extremity fracture and 1,773 claims for those with medical-only dermatitis (Foley et al., 2007). They reported that, CTS claimants only recover to about half of their previous earning levels after six years, compared to the other two groups (Foley et al., 2007).

Physical impacts associated with CTS include sensory deficits that can be painful and restrict the ability to do fine movements, and decreases grip strength (Aboonq, 2015). CTS affects sleep quality including sleep disturbances due to its nocturnal pattern. These physical aspects of CTS potentially lead to further emotional impact on people living with CTS (Foley et al., 2007). These emotional impacts include, but are not limited to, impaired ability to do family and social roles, loss of the individual's ability to contribute to community activities/events, living/working with pain, and ultimately, depression (Foley et al., 2007).

1.4 CTS Management

If diagnosed early, there are many conservative options available to manage CTS. Splinting/orthoses or bracing at nights can be useful as it prevents prolonged wrist flexion or extension and keeps the wrist in a neutral position while sleeping (American Academy of Orthopaedic Surgeons, 2016; Walker, 2013). Education on modifying activities that trigger the signs and symptoms of CTS, mild stretching, and nerve/tendon gliding exercises have been shown to be effective non-surgical treatment options (American Academy of Orthopaedic Surgeons, 2016; Walker, 2013).

In case of a failed conservative treatment, carpal tunnel release (CTR) is the surgical treatment of choice. CTR can be conducted as an open or endoscopic procedure. In both techniques, the aim of the surgery is to cut the transverse carpal ligament to decrease the pressure in the carpal canal, although the endoscopic technique has fewer post-surgery complications (American Academy of Orthopaedic Surgeons, 2016).

The prognosis of the CTR depends largely on the stage of the disease. If a large number of axons have been disrupted and the median nerve is severely damaged, it takes several months for symptoms to improve and recovery can be incomplete (Chammas et al., 2014). The recovery also depends on the age, individual's potential for nerve regeneration and the existence of other comorbidities such as polyneuropathy and systemic disorders (Chammas et al., 2014).

1.5 CTS Diagnosis

Even though CTS is a well-known problem, its diagnosis can still be challenging for clinicians. History taking and observation, clinical examination tests, electrodiagnosis and nerve conduction studies, magnetic resonance imaging, and diagnostic ultrasound are amongst the available diagnostic tools for CTS.

History taking and observation is the first step in diagnosing CTS. History interview topics include the following: sex/gender, ethnicity, bilateral symptoms, diabetes mellitus, worsening of the symptoms at night, duration of symptoms, patient localization of symptoms, hand dominance, symptomatic limb, age, and body mass index (American Academy of Orthopaedic Surgeons, 2016; Bland, 2000; Ibrahim, Khan, Goddard, & Smitham, 2012; Katz et al., 1990).

There is a strong association between frequent complaints of numbness and pain with CTS, according to a study by MacDermid et. al (MacDermid, Kramer, McFarlane, & Roth, 1997). Other studies have reported conflicting results regarding the diagnostic accuracy of history taking. Two high-quality studies (Claes, Kasius, Meulstee, & Verhagen, 2013; Katz et al., 1990) compared history taking to electrodiagnosis for CTS diagnosis. These studies concluded that each item listed above, when collected individually, has a poor discriminative ability to rule in or rule out CTS.

Therefore, clinically it makes more sense to collect these items together, not separately. After discussing subjective characteristics and possible associated pathologies and differential diagnoses, a clinician then decides on the appropriate complementary examinations.

1.4.1 Electrodiagnosis

Electrodiagnostic tests are one of the most commonly used diagnostic tests for CTS. Electrodiagnosis can be in two forms: 1) Nerve conduction velocity studies, testing the conduction velocity of a nerve, or 2) Electromyography (EMG), measuring the electrical activity of a muscle, at rest and when contracted, using surface or needle electrodes (Fuller, 2005). Electrodiagnostic tests, especially nerve conduction studies, are often used as the reference standards in diagnostic studies, despite the fact that these tests have false positive and negative results, possibly due to unstandardized diagnostic criteria (American Academy of Orthopaedic Surgeons, 2016). Different techniques have been reported to have different diagnostic properties, but the most sensitive method is to compare median nerve velocities to another nerve segment of the same person. This method has a high sensitivity of 80 to 92%, and a high specificity of 80 to 99% (Ibrahim et al., 2012).

It is important to note that the results from electrodiagnostic tests should be read in combination with a careful history taking and clinical examination tests. Electrodiagnosis tests are expensive and take from 15 minutes to one hour to complete. In addition, the test can be painful and require patient's cooperation for its completion. 25% of people with clinical complaints of CTS, might have normal nerve conduction values (Witt, Hentz, & Stevens, 2004). In most cases,

if a clinician can localize the lesion using a comprehensive clinical examination, there's no further need to conduct electrodiagnostic tests (Fuller, 2005)

1.5.2 Magnetic Resonance Imaging

Magnetic resonance imaging use strong magnets to create a magnetic field (de Jesus Filho et al., 2014). It's a non-invasive technique and creates three-dimensional images of the soft tissues (de Jesus Filho et al., 2014). Using magnetic resonance imaging for CTS diagnosis first started in 1987 (Middleton et al., 1987). When compared to the Katz hand symptom diagram and nerve condition studies, Magnetic resonance imaging has low specificity (28%) to rule out CTS (Jarvik et al., 2002). This test can be an excellent diagnostic test for rare pathological causes of CTS, such as bony deformities, ganglions, and hemangioma (Ibrahim et al., 2012). A high sensitivity of 96% has been reported for sagittal images, which can accurately show the location of the median nerve compression and determine the severity of CTS (Cudlip, Howe, Clifton, Schwartz, & Bell, 2002). Despite this high sensitivity, the specificity of magnetic resonance imaging is very low, at 33 to 38% (Cudlip et al., 2002; Ibrahim et al., 2012). According to the AAOS guidelines, moderate quality evidence supports not using magnetic resonance imaging as a routine test for the diagnosis of CTS (American Academy of Orthopaedic Surgeons, 2016).

1.5.3 Diagnostic Ultrasonography

Ultrasonography is done for both therapeutic and diagnostic purposes. The diagnostic ultrasonography creates sound waves above the hearing threshold that penetrate into the skin by means of a probe (i.e. transducer). According to a recent high quality study by Fowler et al.

(Fowler, Cipolli, & Hanson, 2015), ultrasonography had high sensitivity and specificity values (91% and 94%, respectively) compared to NCS and CTS-6 tests to diagnose CTS. In another high-quality study, when using nerve conduction studies as the reference standard, ultrasonography has moderate sensitivity (62%) in a population with a high pre-exam probability of CTS; and only 29% sensitivity in those with indeterminate clinical diagnosis (Pastare, Therimadasamy, Lee, & Wilder-Smith, 2009). In a study done by Mondelli et al. in 2008. 23.5% of people with clinical signs and symptoms of CTS, remained undiagnosed using US (Mondelli, Filippou, Gallo, & Frediani, 2008). Based on the results of five high quality and seven moderate quality articles, AAOS concluded that US has low discriminative ability to either rule in or out CTS and should not be used as a routine diagnostic tool for CTS (American Academy of Orthopaedic Surgeons, 2016).

1.5.4 Clinical tests

Clinical diagnostic tests for the diagnosis of CTS are categorized into four main groups (American Academy of Orthopaedic Surgeons, 2016).

1) *Provocative tests*, with the most common tests being Phalen's test and Tinel's sign. These tests aim to reproduce the signs and symptoms of CTS through positioning the wrist into flexion or extension position or by the percussion on the wrist (Walters & Rice, 2002). The sensitivity and specificity of the Phalen's test ranges from 67% to 83%, and from 40% to 98%, respectively (Ibrahim et al., 2012). Tinel's sign, has moderate sensitivity values, ranging from 48% to 73%, whilst the specificity values are higher and range from 30% to 94% (Ibrahim et al., 2012). According to the 2016 AAOS guidelines, strong evidence supports that the performance of a single

provocative test does not provide enough sensitivity or specificity to rule in or out the diagnosis of CTS (American Academy of Orthopaedic Surgeons, 2016).

2) *Sensory/motor tests of the median nerve* incorporate the assessment of the musculature or cutaneous sensory deficits of the hand innervated by the median nerve, e.g. the Semmes-Weinstein monofilament and the two-point discrimination, current perception threshold tests (American Academy of Orthopaedic Surgeons, 2016). Moderate evidence supports that using sensory or motor testing, alone, cannot provide enough diagnostic information to rule in or out CTS (American Academy of Orthopaedic Surgeons, 2016).

3) *Diagnostic scales and questionnaires* are more recent addition to the clinical diagnosis of CTS. Examples of diagnostic scales and questionnaires include CTS-6 (Graham, Regehr, Naglie, & Wright, 2006), Boston carpal tunnel questionnaire (Levine et al., 1993), Kamath and Stothard questionnaire (Kamath & Stothard, 2003). These tests inquire about the subjects' sensory sign and symptoms (e.g. tingling, numbness, nocturnal pain) and functional impairments related to CTS. Different sensitivity values have been reported in the studies for different tests, ranging from 35.1% sensitivity of the Boston carpal tunnel questionnaire (Naranjo et al., 2007) to 95% for the CTS-6 test (Fowler et al., 2015). Similar variations in the reported specificities exist in the literature, ranging from 55.6% for Bland's questionnaire (Bland, 2000) to 91% of the CTS-6 test (Fowler et al., 2015). These tests, combined with other clinical diagnostic tests such as those discussed previously, can lead to accurate diagnosis of CTS (American Academy of Orthopaedic Surgeons, 2016).

4) *Hand symptom diagrams/maps* were first developed by Katz and Stirrat in 1990 and categorize the people with suspected CTS in four categories: classic, probable, possible and

unlikely CTS (Katz & Stirrat, 1990). Different variations in interpretation of the hand symptoms diagrams exist in the literature. Some studies have modified the Katz classification and adopted a new system where those with a classic and probably CTS is considered positive, and the other two groups are considered negative (Calfee et al., 2012; O'Gradaigh & Merry, 2000).

1.6 Kamath and Stothard Questionnaire

Kamath and Stothard questionnaire (Kamath & Stothard, 2003) was developed based on a modification from a previous work by Levine (Levine et al., 1993); however, the exact process of the development of this tool was not mentioned (Kamath & Stothard, 2003). The Kamath and Stothard questionnaire has nine questions with yes/no/not applicable answers. Most of the questions inquire about the sensory alterations of the median nerve and the tingling, numbness and painful sensations associated with CTS. Only one questions relates to the functional limitations of the respondents.

This questionnaire has been reported to have high sensitivity and positive predictive value compared to electrodiagnosis in people with confirmed CTS (Kamath & Stothard, 2003). According to another study, those scoring greater than six on this diagnostic tool, do not need any additional testing for confirmation of CTS (87% sensitivity) (Bridges, Robertson, & Chuck, 2010). Moreover, scores of less than 3 are the least likely to be associated with CTS (87% specificity) (Bridges et al., 2010). The results from a recent study (Wang, Buterbaugh, Kadow, Goitz, & Fowler, 2018) were conflicting with the those previously reported about the diagnostic accuracy of Kamath and Stothard questionnaire. In this study, only a moderate sensitivity of 74% (68-79, 95% CI) and specificity of 64 (54-72, 95% CI) were reported (Wang et al., 2018).

An analysis of the current iteration of the Kamath and Stothard questionnaire by Edwards revealed that the sensitivities of the questions in this questionnaire range from 45.45% to 94.67%, the specificities range from 40% to 100%, positive predictive values range from 76.19% to 100%, and the negative predictive values range from 14.29% to 71.43% (Edwards, 2015).

Questions one, two and three ask about diurnal and nocturnal pain, tingling, and numbness in the wrist and hand area. Feelings of burning pain is one of the complaints in the early stages of CTS (Aboonq, 2015). Due to the possibility of a prolonged poor posture of wrist (excessive flexion or extension during sleeping at night, the pain sensation is often considered to be nocturnal (Luchetti et al., 1989). Tingling and numbness are feelings of pins and needles and heaviness, respectively. These two sensory symptoms are the most common features of CTS (Aboonq, 2015; American Academy of Orthopaedic Surgeons, 2016; Katz & Stirrat, 1990).

One of the widely accepted theories explaining the nocturnal tingling and numbness sensations associated with CTS is the fluid retention or redistribution of body fluids while sleeping or lying position (McCabe, Uebele, Pihur, Rosales, & Atroshi, 2007). Lying posture accompanied with prolonged wrist flexion or extension increase the pressure the carpal canal. This increased pressure leads to the pressure on the median nerve and exacerbates tingling and numbness (McCabe et al., 2007).

Question four asks about movements or postures that people with CTS have adopted to relieve their signs and symptoms (Kamath & Stothard, 2003). The current iteration of this question has a low negative predictive value of 42.42% (Edwards, 2015).

Question five inquires on one of the main differential diagnoses of CTS, which is the ulnar nerve involvements (Aboonq, 2015; Kamath & Stothard, 2003; McCabe et al., 2007). Cutaneous

sensation of the little/5th digit is provided by the ulnar nerve; therefore, in the classic CTS, the little finger is not involved. This question had moderate sensitivity (64%), high specificity (76%), high positive predictive value (88.89%), and low negative predictive value (41.3%).

Question six is the only question in the Kamath and Stothard questionnaire that assesses functional aspects associated with CTS (Kamath & Stothard, 2003). It has a high sensitivity and positive predictive value of 85.33% (Edwards, 2015). Holding the wrist in a prolonged flexion or extension position leads to an elevated pressure within the carpal canal and this rise in pressure in turn, elicits CTS signs and symptoms (Keir, Bach, Hudes, & Rempel, 2007).

Question seven is based on another differential diagnosis of CTS, which is cervical neuropathy (Kamath & Stothard, 2003). Although it has a high specificity and positive predictive value of 100% (Edwards, 2015), the negative predictive value is very low (14.29%). Therefore, more questions could be added to this questionnaire for ruling out CTS. Those with neck pain may require further diagnostic investigations, even if classical CTS symptoms are present.

Question eight might not be applicable to all the respondents as it asks about worsening of the symptoms during pregnancy (Kamath & Stothard, 2003). A CTS prevalence of 34% in a cohort of 639 pregnant participants has been reported (Meems et al., 2015). This increased prevalence of CTS in pregnant women might be due to the increased blood pressure and the lymphoedema associated with pregnancy.

Lastly, question nine asks about improvements of the CTS signs and symptoms, using immobilization and maintaining the wrist in the neutral position. Night splints are amongst the first treatment modalities prescribed for CTS (Page, Massy-Westropp, O'Connor, & Pitt, 2012).

1.7 Analytical Approach Central to the Thesis

Analytical approaches of diagnostic tests accuracy incorporate 2 x 2 contingency tables to extract information about sensitivity, specificity, positive and negative predictive values and likelihood ratios. The sensitivity of a diagnostic test indicates the ability of the tests to truly identify individuals with a disease (i.e. true positive); and specificity is the ability of a test to rule out those individuals without the condition (i.e. true negative) (Jaeschke & Guyatt, 1994).

Positive predictive value is the probability that people diagnosed with a test, truly have that condition; and negative predictive value is the probability of a negative diagnosis with a negative test (Jaeschke & Guyatt, 1994). Positive and negative predictive values are affected by the prevalence of a disease in a population, so we tried to extract or calculate positive and negative likelihood ratios which are independent of the prevalence (Sedighi, 2013). Likelihood ratios are the likelihood that someone with a positive or negative diagnosis according to a diagnostic tool, actually has the true positive or true negative results.

The formulas to calculate these diagnostic properties are as follows (Jaeschke & Guyatt, 1994):

- I. Sensitivity= true positive/ (true positive + false negative)
- II. Specificity= true negative/ (true negative +false positive)
- III. Positive predictive value= true positive/ (true positive + false positive)
- IV. Negative predictive value= true negative/ (true negative + false negative)
- V. Positive likelihood ratio= sensitivity/ 1-specificity
- VI. Negative likelihood ratio= 1-sensitivity/ specificity

In the third chapter of this dissertation we did a qualitative content analysis to interpret the qualitative data from cognitive interviews in the third chapter (Knafl, Deatrick, Holcombe, Bakitas & Dixon, 2007). We incorporated a framework developed by MacDermid that categorizes the errors in responses from cognitive interviews in six categories (MacDermid, 2018).

1.8 Current Gaps in the Literature regarding CTS Diagnosis

Making an accurate diagnosis is essential for implementing an appropriate plan of care for any given condition. Due to the high prevalence of CTS, the diagnosis of this condition is an important matter to the clinicians. The variety and a large number of available diagnostic tests and studies also reflect back on the importance of this issue. In fact, no other clinical condition seen by the hand therapists has this variety of available clinical diagnostic tests (MacDermid & Wessel, 2004). If not diagnosed early, CTS can cause severe irreversible damage to the median nerve, with the symptoms remaining even after the carpal tunnel release surgery. The early and accurate diagnosis would also decrease the need for potential future surgical treatment and avoid post-surgical complications, decreasing patient, societal and health care burden.

Despite the high prevalence and importance of CTS, there is still no consensus over a diagnostic gold standard (American Academy of Orthopaedic Surgeons, 2016). The diagnostic process usually starts with a classical approach of gathering information from history taking and clinical diagnostic tests and deciding on a further need for a complementary diagnostic test (Graham, 2008; MacDermid & Wessel, 2004). In some clinical settings, almost always electrodiagnostic tests are conducted, whereas, in some others, these tests are barely used (Graham, 2008). These differences and variations in the process of decision making for CTS diagnosis are

highly attributable to the lack of a gold standard. In clinical medicine, we often use the term *gold standard* to indicate a definite diagnosis (Graham et al., 2006). Nonetheless, the establishment of a gold standard requires consensus, and a test with high sensitivity and specificity values. Usually, electrodiagnosis is taken as the gold standard test for CTS, whereas there's no agreement or consensus regarding this matter (American Academy of Orthopaedic Surgeons, 2016). The role of electrodiagnosis for CTS is undeniable; however, they cannot be performed as the sole diagnostic test in all circumstances (American Academy of Orthopaedic Surgeons, 2016), which is a mandatory feature of any given gold standard diagnostic test.

Lack of a diagnostic gold standard for CTS, in turn, affects a hand therapists' ability to determine proper treatment, delays interventions, and requires inappropriate and unnecessary imaging or special tests and exams. As a result, the plan of care varies considerably for people suspected of CTS in different settings according to the background of the treating clinician (Graham, 2008).

According to our literature search, diagnostic questionnaires and scales can be useful and potentially highly accurate in the diagnosis of CTS. They do not require highly advanced technology, high level of expertise, time and money, and are more tolerable by the subjects. CTS diagnostic questionnaires are very brief and have 9 (Kamath & Stothard, 2003) to 19 items (Levine et al., 1993).

The previous systematic review of clinical diagnostic tests for CTS is outdated (MacDermid & Wessel, 2004), and does not include any of the recently developed tests, such as Wainner clinical prediction rule (Wainner et al., 2005), CTS-6 (Graham et al., 2006), and Lo carpal tunnel prediction rule (Lo, Finestone, & Gilbert, 2009). Moreover, the Kamath and Stothard

questionnaire has conflicting diagnostic accuracy properties reported in four different studies (Bland, Weller, & Rudolfer, 2011; Bridges et al., 2010; Kamath & Stothard, 2003; Wang et al., 2018). Part of the inconsistencies in the reported diagnostic accuracy values of the Kamath and Stothard questionnaire might be the lack of a content validation study. Content validity is the extent that a diagnostic questionnaire is measuring the constructs and concepts that is supposed to measure (Terwee et al., 2018). Validation of this questionnaire can potentially lead to an improved diagnostic accuracy properties (Willis, 2004).

1.9 Thesis Objectives and Composition of Papers

This dissertation will address the lack of a comprehensive and up-to-date systematic review of diagnostic test accuracies of clinical questionnaires, scales, and hand symptom diagrams for the diagnosis of CTS. We also did a content validation study on the Kamath and Stothard questionnaire, aiming to improve the psychometric properties. One way to measure content validity is to do cognitive interviews (Willis, 2004).

These objectives were addressed in two sub-studies with their own specific purposes, addressed in two individual manuscript using the research approaches listed below. These two studies were performed as part of the requirements for the School of Rehabilitation Sciences Master's program at McMaster University.

Manuscript 1 (Second chapter) - Study Design: a systematic review of diagnostic test accuracy

The specific research purpose was to provide a review, appraise and synthesize the evidence on the diagnostic accuracy of clinical scales, questionnaires and symptom diagrams/maps for the diagnosis of CTS amongst people presenting with suspected CTS. The sources of information of this study were three databases, in which we extracted data by developing a search strategy in consultation with a health science librarian.

Manuscript 2 (Third chapter) - Study Design: qualitative (cognitive interviewing)

The primary aim of this study was to describe how persons experiencing hand symptoms and expert clinicians or researchers understand and respond to items on the Kamath and Stothard Questionnaire for carpal tunnel syndrome diagnosis. In this study, we received ethics approval from HiREB and conducted cognitive interviews with eighteen participants to reach data saturation.

Together, these papers advance the literature and our understanding of diagnostic accuracy tests for carpal tunnel syndrome. The final chapter provides a discussion of the overall findings and the contribution this body of work makes to rehabilitation science and clinical professions related to the diagnosis of CTS. In summary, the research in this dissertation attempts to address the lack of a comprehensive systematic review of clinical questionnaires, scales, and hand diagrams/maps. It also validates a questionnaire that already has a moderate to high diagnostic accuracy, to further advance the body of literature available on this test.

1.10 References

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**Chapter Two: Diagnostic Accuracy of Scales, Questionnaires and
Hand Symptom Diagrams for the Diagnosis of Carpal Tunnel Syndrome:
A Systematic Review of Diagnostic Test Accuracy**

Title: Diagnostic Accuracy of Scales, Questionnaires and Hand Symptom Diagrams for the Diagnosis of Carpal Tunnel Syndrome: A Systematic Review of Diagnostic Test Accuracy

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Acknowledgement: Joy MacDermid was supported by a Canadian Institutes of Health Research Chair in Gender, Work and Health and the Dr. James Roth Chair in Musculoskeletal Measurement and Knowledge Translation.

2.0 Abstract

Study Design: Systematic review of diagnostic test accuracy

Background: Carpal Tunnel Syndrome CTS is the most prevalent compressive neuropathy of the upper extremity. Good clinical tests can support accurate diagnosis and management of CTS.

Objective: To summarize and evaluate research on the accuracy of clinical diagnostic scales, questionnaires and hand symptom diagrams/maps (HSD) used for diagnosis of CTS.

Methods: A comprehensive literature search of MEDLINE, CINAHL, and Embase databases, using keywords related to the diagnostic accuracy of CTS, was conducted on August 2, 2018. PRISMA guidelines were followed. Quality assessment of bias and applicability was conducted using the QUADAS-2 tool. Diagnostic accuracy properties, including sensitivity, specificity, likelihood ratios, and 95% confidence interval, were summarized.

Results: Out of 5552 citations, 21 articles met the inclusion criteria. Twelve articles reported on the diagnostic accuracy of scales and questionnaires: Bland questionnaire (n=3), Kamath and Stothard questionnaire (n=3), CTS-6 (n=3), Boston carpal tunnel questionnaire (n=2), Wainner clinical prediction rule (n=1), Lo carpal tunnel prediction rule (n=2). Positive likelihood ratios (LRs) to diagnose or rule in CTS ranged from 0.94 for Boston carpal tunnel questionnaire to 10.5 for CTS-6 scale, and negative LR to exclude or rule out CTS ranged from 1.05 to 0.05 for the same diagnostic tools. Nine studies were identified on the diagnostic accuracy of Katz and

Stirrat HSD. Positive and negative LR_s ranged from 1.42 to 8, and from 0.78 to 0.05, respectively. Only four studies had high methodologic quality.

Conclusion: Limited evidence supports high accuracy of CTS-6, Kamath and Stothard questionnaire, Bland questionnaire, and Katz and Stirrat's HSD. Other scales have lesser and more conflicting evidence. Further high-quality studies are necessary to examine the diagnostic accuracy of these tests to assist ruling in or out for CTS.

Level of evidence: Diagnostic, level 3b

Keywords: carpal tunnel syndrome, diagnostic accuracy, physical examination tests, diagnostic scales and questionnaires, hand symptom diagram/map

2.1 BACKGROUND

Carpal Tunnel Syndrome (CTS) is caused by compression of the median nerve in the carpal canal and is the most prevalent type of compression neuropathy of the upper extremity (UE). The prevalence of CTS has been estimated to be 6% in men, and 9.2% in women.¹ Symptoms include pain, tingling and numbness in the palmar surface of the first three digits (the area innervated by the median nerve), as well as thenar muscle weakness and hypotrophy in more severe instances¹. CTS is a significant contributor to days lost from work, with one study finding an average of \$45,000–\$89,000 per claimant in the USA in the period from 1990 to 2001².

A significant barrier to the treatment of CTS is the lack of a diagnostic gold standard³. Clinical decision making is an ongoing process to gather enough information to decide on the optimal plan of care⁴, with the identification of a diagnosis or health problem as a central feature. Clinical examination tests are quick, inexpensive, and give an immediate answer, which makes them appealing for the diagnosis of CTS. Even though the diagnosis of CTS can be made through a variety of clinical examination tests and history taking³, the final confirmation is often made based on neurophysiological tests assessing the median nerve conduction velocity⁵. The most recent CTS management guideline of the American Academy of Orthopedic Surgeons (AAOS), concludes that only limited evidence supports the use of hand-held Nerve Conduction Studies (NCS), ultrasound and MRI in CTS diagnosis³. These advanced diagnostic testing can be

expensive, and in some cases (e.g. NCS) painful. Moreover, although a common tool in CTS diagnosis, electrodiagnostic studies have concerning false positive and negative results when compared to clinical examination tests³.

According to a previous systematic review done by one of the authors of this study (JM)⁶ and the AAOS guideline³, clinical examination tests for the diagnosis of CTS can be categorized into four major groups: 1) Provocative maneuvers (e.g. Phalen test, Tinel sign), 2) Sensory and motor tests (e.g. Two-point discrimination, Thenar weakness test), 3) Diagnostic scales (e.g. CTS-6) and questionnaires (e.g. Kamath and Stothard questionnaire), and 4) Symptom Diagrams/Maps (Katz and Stirrat's HSD). Due to the number of tests, and accumulation of studies addressing these tests and the variations in test techniques, it was decided to conduct this systematic review (SR) on diagnostic scales and symptom diagrams/maps. Diagnostic reviews addressing the two other categories (provocative and sensory/motor tests) will be presented in two separate SRs⁷.

The last SR on this topic published by MacDermid and Wessel in 2004⁶ is outdated. The purpose of this study was to provide a review, appraise and synthesize the evidence on the diagnostic accuracy of clinical scales, questionnaires and SDs for the diagnosis of CTS amongst people presenting with suspected CTS.

2.2 METHODS

We registered this study with the International Prospective Register of Systematic Reviews (PROSPERO) a database of systematic review protocols for health and social topics on December 20, 2019 (CRD42018109031). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane collaboration guidelines were followed^{22,23}.

2.2.1 Information Sources

We conducted a literature search in four electronic databases: MEDLINE (through Ovid from 1946), Embase, the Cochrane Database of Systematic Reviews and CINAHL from their inception to August 2, 2018. The search strategy was designed to identify studies of diagnostic test accuracy of at least one clinical diagnostic test for the diagnosis of CTS, though, for this SR, we only reported the results for the diagnostic scales, questionnaires and HSDs. We developed the search strategy in two consecutive meetings with a librarian specialized in health science research methodology at McMaster University, combining the vocabulary and keywords related to the diagnostic accuracy of the clinical examination tests for the diagnosis of CTS. The names of the clinical diagnostic tests for CTS were extracted from multiple sources. Firstly, we explored the previous systematic and narrative reviews of diagnostic test accuracy of physical examination tests for the diagnosis of CTS and the AAOS guidelines. Secondly, the terms used for the search strategy were reviewed by two authors of this study, a physiotherapist and a hand therapist (AD, JM) to ensure that all known physical examination tests were included. As the goal of this review was to be as comprehensive and accurate as possible, we also hand searched the reference lists of the included articles. The full search strategy for the MEDLINE, CINAHL, and Embase databases are presented in the appendix.

2.2.2 Study Selection

Two reviewers (AD, JY) performed the study selection independently in two phases. In the first phase, titles and abstracts were reviewed against pre-determined inclusion and exclusion criteria. AD and JY initially reviewed the first 100 titles and abstracts and resolved their disagreement through discussion to increase the quality of the selection process. The agreement of the reviewers in this phase was calculated using kappa statistics.²⁴ Kappa values of less than 0.20 indicate poor agreement and the values of more than 0.80 indicate almost perfect agreement in rating²⁴. All statistical analyses were conducted using STATA 15 software²⁵. In the second phase, full-text articles were retrieved and reviewed. In case of any disagreement at the first or second phase of the study selection process, a third reviewer (the most experienced member: JM), moderated a consensus through discussion.

2.2.3 Eligibility Criteria

There were no restrictions on study selection based on sample size, language or gender of the study sample. Studies were included in this systematic review if the below criteria were met:

Design: systematic reviews, case-control, cross-sectional, or cohort studies, with either prospective or retrospective data collection in a full-report format.

Participants: adults ≥ 18 years old; diagnosed or suspected with CTS, as well as control groups to the CTS patients, who are people with any diagnosis of neurological, musculoskeletal and vascular manifestations of the upper extremity (e.g. cervical radiculopathy or tennis elbow).

Diagnostic test: studies that assessed at least one diagnostic accuracy property of the physical examination tests for the diagnosis of CTS (restricted to diagnostic tests scales and hand symptom/maps).

Comparison: since there is no known gold standard for the diagnosis of CTS, a decision was made to compare the physical examination tests to any reference standard used in each study's design, such as, nerve conduction studies, surgical decompression of carpal canal, other clinical examination diagnostic tests, or a combination of reference standard tests made by a physician or expert clinician.

Outcome: articles reporting diagnostic accuracy properties, such as, sensitivity and specificity, likelihood ratio, or that provided enough data to (re-)construct 2X2 contingency tables.

Time: all time frames reporting diagnostic accuracy of clinical examination for the diagnosis of CTS.

The following exclusion criteria were applied: 1) Reviews, letters, conference abstracts, editorials, case reports; 2) Studies not using diagnostic scales, questionnaires or HSDs as an index test for the diagnosis of CTS; 3) Studies on other median nerve conditions other than CTS; 4) Studies not reporting sensitivity, specificity or other diagnostic accuracy properties, or not providing enough data for it to be possible to calculate them.

2.2.4 Data Extraction

Two authors (AD, JY) independently extracted information from three included articles and the agreement was discussed with a third author (JM). Since the agreement was very high, AD did the rest of the data extraction process using a pre-determined, self-developed data extraction form. In case of any uncertainty in data extraction, JY and JM were contacted and a consensus acquired through discussion. The extracted data consisted of the following information: author identification, publication year, country of study, study design, participants characteristics (age,

gender, CTS severity and duration), sample size, inclusion and exclusion criteria and participants selection process, clinical examination test, reference standard, and all of the available information regarding diagnostic accuracy measures. In case of any values missing from the articles, the authors were contacted by email.

2.2.5 Data synthesis and analysis

Where possible, we extracted sensitivities, specificities, positive and negative predictive values (PPV, NPV), as well as positive and negative likelihood ratios (+LR, -LR). When data was not provided, we tried to calculate values, using the information reported about true positives, false positives, false negatives, and true negatives²⁶. We then created 2X2 contingency tables and calculated the sensitivity, specificity, +LR, and -LR, including the 95% confidence interval (CI) for each physical examination test, if possible²⁶. The sensitivity of a diagnostic test is the ability of the test to truly label people (i.e. true positive) with a given medical condition, and specificity of a diagnostic test is defined as the identification of those without the disease or disorder (true negative)²⁶.

Likelihood ratios are diagnostic accuracy properties that are independent of the prevalence of the disease²⁷. We calculated +LR as: $\text{sensitivity}/(1-\text{specificity})$, and -LR was calculated as $(1-\text{sensitivity})/\text{specificity}$ ²⁷. +LR values of greater than 10, and -LR less than 0.1 are one of the most useful measures in diagnostic decision making²⁷. Values between 5 to 10 of +LR and 0.1 to 0.2 of -LR suggest the test has moderate ability to change the probability of having a condition³. Lastly, values of less than 5 or more than 0.5 of +LR and -LR, respectively, suggests the test has a small ability to change the probability of a diagnosis³. Data heterogeneity (e.g. different index tests,

different sample characteristics, different cut-off points for positive test results) precluded the conduction of a meta-analysis.

2.2.6 Assessment of risk of bias

Two independent authors (AD, JY) independently rated the risk of bias and applicability concerns using the QUADAS-2²⁸ (Quality Assessment of Diagnostic Accuracy Studies, revised version) tool. In case of any discrepancies, we reached a consensus through discussions with JM. The QUADAS-2 tool rates the risk of bias of the articles in four domains: participant selection, index test, reference standard, and flow and timing²⁸. The applicability concerns regarding the articles are rated for all of the domains in QUADAS-2 tool except for the flow and timing of the participants²⁸. Each domain has a set of signalling questions that can be answered as yes, no, or unclear²⁸. If the answers to all of the signalling questions were yes, then that domain was considered to have a low risk of bias or applicability concerns. If the answer to any of the signalling questions of a domain was no or unclear, the risk of bias or applicability concerns of that domain was rated as high or unclear. To generate an overall rating on the risk of bias or applicability concerns of an article, studies rated as low on all of the domains acquired a “low risk of overall bias” or “low applicability concerns”. Furthermore, ratings of high or unclear on any of the domains resulted in the overall judgment of the articles as “at risk of bias” or “concerns regarding applicability”.

2.3 RESULTS

2.3.1 Selection of Studies and Methodological Assessment

Figure 1 illustrates the results of the systematic search and study selection process according to the PRISMA statement²³. After the removal of the duplicates and the evaluation of the 5552 hits, only 161 references were found to be potentially eligible by the predefined eligibility criteria, which were then assessed in the second phase of screening (full-text review). Twenty-one articles met the inclusion criteria of this SR, with nine studies assessing the diagnostic accuracy of diagnostic symptom diagrams/maps^{19,29–36} and twelve articles reporting on the diagnostic accuracy of diagnostic scales and questionnaires^{1,23–32}. The studies were conducted in six countries: Austria, Canada, Greece, Spain, UK and USA. Conflicts of interest of the included studies are available in Appendix B. The kappa value of the agreement of the two reviewers in screening the titles and abstracts of this SR was calculated to be 0.70 (SE: 0.02). The methodological assessments of all of the included articles are presented in Figure 2.2, and the assessment of each individual study methodology based on the QUADAS-2 tool is illustrated in Figure 3. Overall, four studies had a low risk of bias^{14,17,33,34}, and four had unclear rating only in one domain^{9,21,30,37}. According to applicability, twelve studies had no concerns^{9,10,34,37,12–14,16,17,21,30,33}.

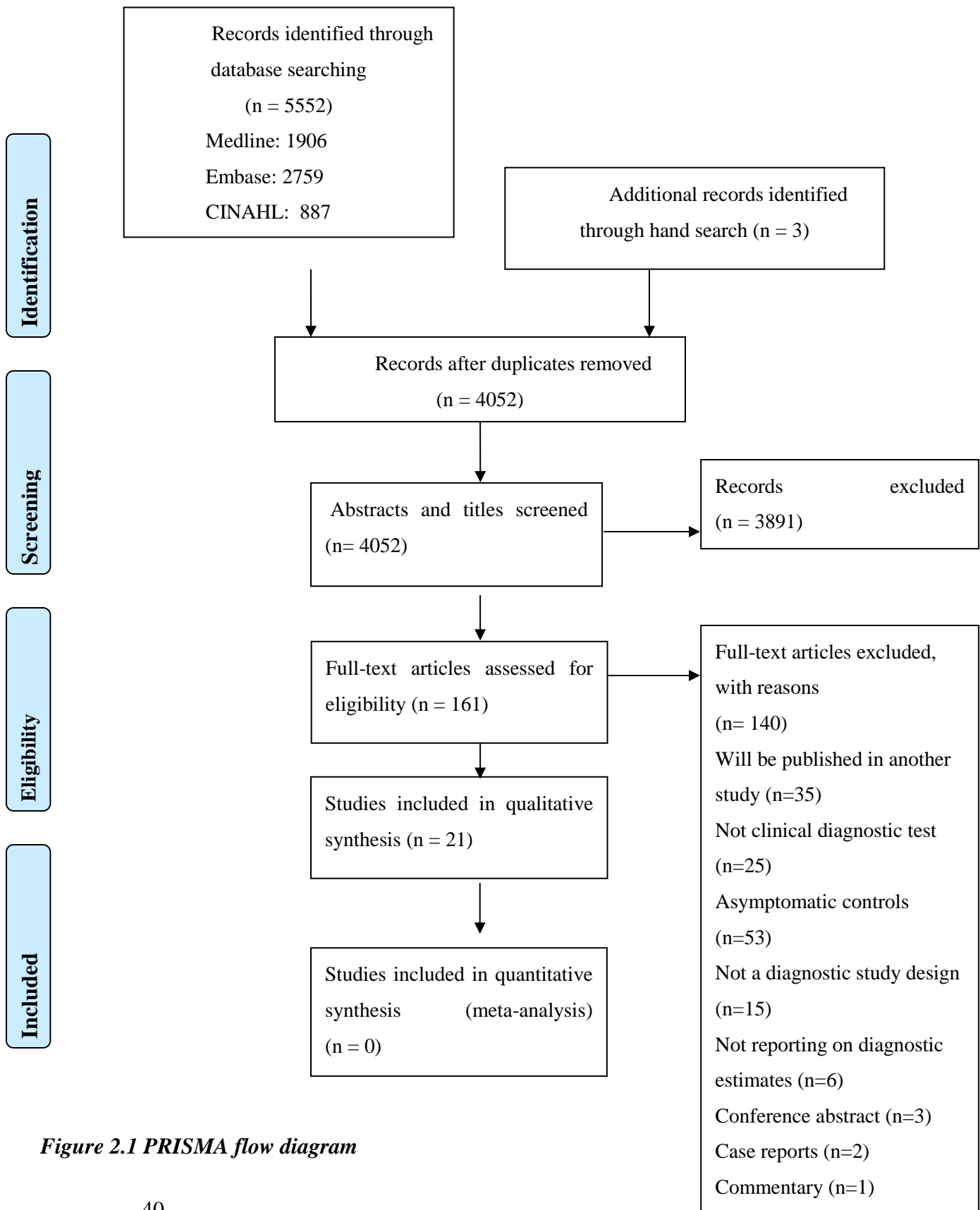


Figure 2.1 PRISMA flow diagram

The detailed characteristics of the participants of the included studies, as well as the clinical diagnostic tests utilized and the reference standards of each study are presented in Tables 2.2 and 2.3. The majority of the included studies had a prospective cross-sectional study design, except for three articles^{9,19,37} which had retrospective study designs. Almost all of the studies recruited their sample from persons with suspected CTS referred to orthopedic, rheumatology, hand clinics (or similar clinical settings), or nerve conduction labs, except for three studies³⁰⁻³² that recruited their participants from workers with suspected or at risk of CTS. Only three studies reported the pre-exam probability of having CTS in their study sample^{9,32,36}. Due to the high variability among studies, e.g. a variety of index tests, criteria for positive test results, and population characteristics, the information could not be pooled to do a meta-analysis.

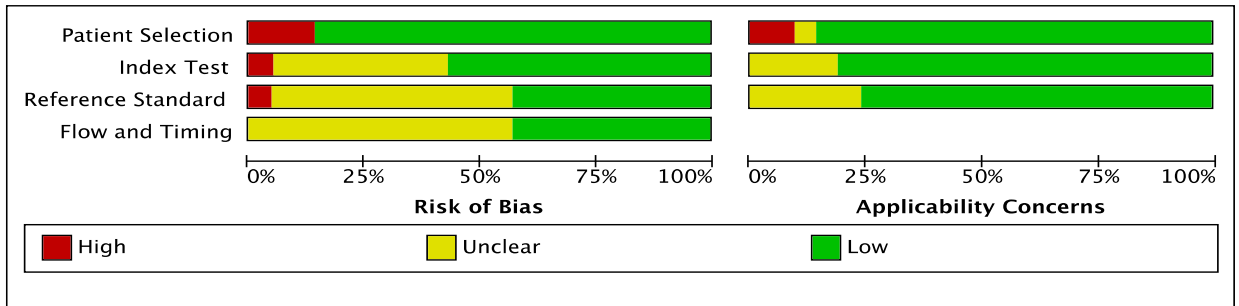


Figure 2.2 The proportion of included studies with low, high, or unclear risk of bias and concerns regarding the applicability, using QUADAS-2 tool

2.3.2 Diagnostic Accuracy of the diagnostic Scales and Questionnaires for CTS diagnosis

Eight different diagnostic tools were utilized and assessed across all of the included studies. Of the 11 studies on the diagnostic accuracy of the scales and questionnaires for the diagnosis of

CTS, the following diagnostic tools were assessed: 1) Bland Questionnaire¹⁴⁻¹⁶; 2) Kamath and Stothard questionnaire^{1,20,21,37}; 3) CTS-6 diagnostic scale^{1,10,37}; 4) Boston carpal tunnel questionnaire^{12,13}; 5) Lo carpal tunnel prediction rule^{1,17}; 6) Wainner clinical prediction rule¹. A thorough description of the CTS Diagnostic scales, questionnaires and HSDs are presented in table 2.1.

The overall sample size of these studies was 17,768 (wrists with suspected CTS), with 7,488 wrists diagnosed with true positive CTS (positive results confirmed by both the index and the reference standard tests). Positive LR to diagnose or rule in CTS ranged from 0.94 for Boston carpal tunnel questionnaire¹³ to 10.5 for CTS-6 scale⁹, and Negative LR to exclude or rule out CTS ranged from 1.05 for Boston carpal tunnel questionnaire¹³ to 0.05 for CTS-6 scale⁹ (Table. 2.4). Only one study combined tests, which resulted in high sensitivity (95.5%) and moderate specificity (50%)³⁷.

Table 2.1 Description of Scales, Questionnaires and Hand Symptom Diagrams for Carpal Tunnel Syndrome

Diagnostic Test	Method	Positive Result Threshold
CTS-6 Diagnostic scale ⁸	Six criteria are assessed and scored, which are: 1. Numbness in the median nerve distribution (3.5 points) 2. Nocturnal numbness (4 points) 3. Thenar musculature weakness/ atrophy (5 points) 4. Tinel’s sign (4 points) 5. Phalen’s test (5 points) 6. Loss of 2-point discrimination (4.5 points)	1. A score of 12 points (50%) ⁹⁻¹⁰ 2. A score of 18 points ¹
Boston carpal tunnel questionnaire ¹¹	Is comprised of two subscales, one is measuring the severity of symptoms (SSS) through 11 questions, another one looking at the functional status (FSS) of people with CTS (8 questions of hand function during daily activities).	1. Scores of 1.95 or greater ¹² 2. Scores of 3 or greater ¹³
Bland’s questionnaire ¹⁴	Has two sections:	1. A score of 7 or greater ¹⁴ 2. A cut-off probability of 0.5 ¹⁵

	<ol style="list-style-type: none"> 1. Background information including age, occupation, hand dominance and diabetes is recorded. There is an open question regarding the type of symptoms experienced by the patient. 2. Questions 6 to 12 cover details of symptoms including the location of paraesthesia in hand, nocturnal pain, relief of paraesthesia by shaking the hand, relief by the use of a wrist splint, impairment of manual dexterity, and duration of symptoms. 	<ol style="list-style-type: none"> 3. A score of 40% or greater¹⁶
Lo carpal tunnel prediction rule ¹⁷	<p>Nine clinical variables are assessed and scored:</p> <ol style="list-style-type: none"> 1. Gender 2. Duration of symptoms 3. Presence of wrist pain (negative predictor) 4. Presence of neck pain (negative predictor) 5. Nocturnal symptoms, 6. Presence of thenar atrophy 7. Abductor pollicis brevis weakness 8. Median sensory symptoms 9. Pinprick sensation examination. 	A score of 10 or greater ¹
Wainner Clinical Prediction Rule ¹⁸	<p>Five items are assessed and scored:</p> <ol style="list-style-type: none"> 1) Shaking hand and symptoms relief 2) Wrist-ratio index 3) Symptom Severity Scale 4) Reduced median sensory field of digit 1 5) Age greater than 45 y 	A score of 3 or greater ¹
Katz Hand Symptoms Diagram ¹⁹	A self-administered hand symptoms diagram that depicts both hands with dorsal and palmar views. Patients are asked to mark areas on the diagram corresponding to the location of their symptoms and to indicate the quality of their discomfort.	<p>Classic CTS: tingling, numbness, or decreased sensation with or without pain in at least two digits, 1,2, or 3; symptoms in the dorsum and palms of the hands excluded; fifth finger symptoms, wrist pain or radiation proximal to the wrist allowed;</p> <p>Probable CTS: same as classic, except palmar symptoms allowed unless confined solely to ulnar aspect;</p> <p>Possible CTS: tingling, numbness and/or decreased sensation in at least one digit 1,2, or 3;</p> <p>Unlikely CTS: no symptoms in digits 1,2 or 3¹⁹</p>
Kamath and Stothard Questionnaire	Has nine questions asking about signs and symptoms of CTS, with yes, no, not applicable response options.	<ol style="list-style-type: none"> 1. Scores of greater than 6 and below 3²⁰ 2. Score >5^{21,1}

2.3.3 Diagnostic Accuracy of Hand diagrams/maps for CTS diagnosis

Nine studies evaluated the diagnostic accuracy of Katz and Stirrat’s HSD^{19,29–36}, with a sample size of 1796 wrists with suspected CTS and 930 true positive CTS wrists. Positive LR to diagnose or rule in CTS ranged from 1.42³⁰ to 8¹⁹; Negative LR to exclude or rule out CTS ranged from 0.78³² to 0.05³⁴ (Table. 2.5).

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Ammer et al. (1993)	High	Unclear	Unclear	Unclear	High	Low	Unclear
Bland (2000)	Low	Unclear	Unclear	Low	Low	Low	Unclear
Bland et al. (2011)	Low	Low	Low	Unclear	Low	Low	Low
Bland et al. (2014)	Low	Unclear	Unclear	Low	Low	Low	Low
Bonauto et al. (2008)	Low	Low	Low	Unclear	Low	Low	Low
Bougea (2018)	Low	Unclear	Unclear	Low	Low	Low	Low
Bridges et al. (2010)	Low	High	High	Low	Low	Unclear	Unclear
Calfee et al. (2011)	Low	Unclear	Unclear	Unclear	Low	Unclear	Low
Fowler et al. (2015)	Low	Low	Low	Unclear	Low	Low	Low
Franzblau et al. (1994)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Hems et al. (2009)	Low	Low	Low	Low	Low	Low	Low
Kamath and Stothard (2003)	Low	Low	Low	Unclear	Low	Low	Low
Katz and Stirrat (1990)	High	Unclear	Low	Low	Unclear	Unclear	Low
Katz et al. (1990a)	Low	Low	Low	Low	Low	Low	Low
Katz et al. (1990b)	Low	Low	Low	Low	Low	Low	Low
Lo (2009)	Low	Low	Low	Low	Low	Low	Low
Makanji et al. (2012)	Low	Unclear	Unclear	Unclear	Low	Low	Low
Naranjo et al. (2007)	Low	Low	Unclear	Unclear	Low	Low	Low
O’Gradaigh and Merry (2000)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Szabo et al. (1999)	High	Low	Unclear	Unclear	High	Low	Low
Wang (2018)	Low	Unclear	Unclear	Unclear	Low	Unclear	Low

● High
 ● Unclear
 ● Low

Figure 2.3 Risk of bias and applicability concerns of the included studies

2.3.4 Reference standards for CTS diagnosis

17 studies^{10,12,31–37,13–17,20,29,30} used electrodiagnosis as their reference standards, although the methodology and criteria for positive test results varied between the studies. Two studies performed clinical diagnosis^{1,19}; one study²¹ used Carpal Tunnel Release surgery (CTR) as their reference standard. One study did not have a reference standard and compared the results of CTS-6 to NCS and diagnostic ultrasound findings using a statistical method called latent class analysis⁹.

2.4 DISCUSSION

The purpose of our systematic review was to summarize and assess the quality of the diagnostic scales, questionnaires, and symptom diagrams/maps for the diagnosis of CTS. We found twelve clinical studies reporting on six different diagnostic scales and questionnaires, as well as nine studies on Katz and Stirrat's HSD.

Accurate diagnosis is the key to establish appropriate treatment plans and prognosis. Given the high prevalence of CTS, the clinical diagnosis tends to be an important concern for clinicians. Indeed, no other single condition seen by the hand therapists seems to have this variety of available clinical diagnostic tests⁶. The considerable number of available studies on the clinical diagnosis of CTS also reflect the prominent emphasis on the diagnosis of this condition.

The pattern of care of people with suspected CTS varies noticeably in different settings determined by the clinical background of the treating clinician³⁸. A classic approach is to gather information from history and physical examination tests first and create a list of possible diagnoses, then, determining further ancillary testing to confirm one of these diagnoses³⁸. In some clinical settings, electrodiagnostic tests are almost always performed for CTS diagnosis, whereas in some

others, these tests are rarely administered³⁸. The variations in the decision making process on the diagnosis of CTS might highly be due to the lack of a gold standard³. We often use the term *gold standard* in clinical medicine to imply a definite diagnosis of a given condition. Nonetheless, gold standards can only be established by consensus⁸. With that being said, the presence of agreement is the key to establish a standard of diagnosis⁸. Electrodiagnosis is often considered the gold standard in the diagnosis of CTS, although there is no agreement on this issue⁸³. It is noteworthy to consider that electrodiagnostic tests do play a role in the diagnosis of CTS. However, they cannot be performed, alone as the gold standard for the diagnosis in all circumstances³, which is an essential feature of any gold standard diagnostic test⁸.

The available clinical examination tests for the diagnosis of CTS can be categorized into four main groups, each test having limited capability of being used alone as the diagnostic criteria to rule in or rule out CTS. In practice, diagnosis is often a triangulation of a representative test from several of the four main categories: that is, provocative tests, sensorimotor tests, and the self-reported questionnaires of symptoms or clinician-based evaluations described herein. Following is a discussion of the available scales, questionnaires and hand symptoms/maps.

2.4.1 Scales and questionnaires to diagnose CTS

The two tests that were most frequently studied in the literature were the CTS-6 and the Kamath and Stothard diagnostic tests. The CTS-6 test is comprised of six criteria which were found to be highly contributing to the diagnosis of CTS, as ranked by a Delphi consensus of a panel of expert clinicians⁸. These criteria and the positive threshold criteria across the included studies are explained in Table 1. In one of the included studies in our SR³⁷, they called this test *CTS-7*;

however, the rationale behind this naming is unclear, and they have referenced the CTS-6 paper⁸. By using CTS-6 to calculate the pre-test probability of CTS, electrodiagnostic testing may not be needed in many cases of CTS and adds little value in decision making about the diagnosis of this condition³⁸.

Kamath and Stothard stated they developed a questionnaire based on the previous work of Levine¹¹; however, a clear description of this process is lacking²¹. Despite this shortcoming in validation, one high-quality paper²⁰ as well as two papers^{21,37} with unclear ratings in only one domain, have assessed the diagnostic accuracy properties of this tool. In the original Kamath and Stothard article, only persons with a definite diagnosis of CTS (determined by CTR) were included, therefore values of specificity and negative predictive value, and in extension positive and negative LR's could not be calculated²¹. High diagnostic accuracy values have been reported in two studies^{20,21} (Sensitivities: 85-87%, Specificity: 87%), and further validation of the Kamath and Stothard questionnaire might lead to increased diagnostic strength of this test.

The Boston Carpal Tunnel Questionnaire (BCTQ), a tool most frequently used as an outcome measure for the CTS treatment, was also assessed in two studies^{12,13}. According to the likelihood ratios of these two studies, BCTQ had a small value in predicting the possibility of having true positive CTS diagnosis. BCTQ is called different names across the studies (e.g. Levine's questionnaire²¹); however, all of these names refer to the same diagnostic test¹¹.

The Bland questionnaire was evaluated in three studies, two with large samples^{15,16} and one high-quality paper¹⁴. Compared to NCS as the reference standard, Bland questionnaire had strong sensitivity and positive predictive values (80% and 92%, respectively)¹⁴; therefore, we suggest it might be a good tool to rule-in CTS, but is not very specific in ruling it out. Two clinical

prediction rules, Lo carpal tunnel prediction rule and Wainner clinical prediction rule, were studied in one of the included articles¹. The reference standard of this study was not well-defined, and the extracted information is at risk of bias¹. The Lo carpal tunnel prediction rule was assessed in another high-quality study; however, the results indicated only moderate sensitivity (76%) and specificity (68%) are predictable when EDS is the reference standard.

2.4.2 Hand symptoms diagrams/maps to diagnose CTS

Nine studies comparing Katz HSD to a reference standard in people with suspected CTS were found in the literature and summarized in Tables 2.3 and 2.5. Three different criteria for positive test interpretation were identified in the included studies. Six studies categorized the people with suspected CTS into four groups of classic, probable, possible and unlikely (Table 2.1), which is the original categorization method suggested by Katz and Stirrat in 1990¹⁹. This categorization resulted in the highest +LR and lowest -LR amongst all of the included studies¹⁹. Two studies interpreted people in classic or probable categories as having positive, and those in possible or unlikely categories as negative CTS diagnosis^{35,39}. Finally, one article interpreted those with classic, probable, and possible results according to the diagram as having CTS, and those in the unlikely category as not having CTS; this categorization led to the small ability of this test to indicate the change in the probability of having or not having CTS in this study³⁰.

Due to the lack of a diagnostic gold standard for CTS³, different reference standards were used in the included studies. A decision was made to include the studies regardless of their choice of reference standard⁷. The most common reference standard test used in the included studies was

electrodiagnosis; however, this comparison is unsound because electrodiagnosis evidently has false positive and negative results³. Only one study used Latent Class Analysis⁹ (LCA), which is a statistical technique that can be used when there is no established gold standard. In this study, the latent variable was assumed to have two outcomes, which were positive and negative test results⁹.

Only three studies reported the prevalence of CTS in their sample^{9,32,36}. Settings with a higher prevalence of CTS, e.g. hand clinics or electrodiagnosis labs, have higher pre-test probability of CTS. It is important to consider the setting in which the study is being conducted. Although the results from the studies done in a clinical setting tend to be closer to what a clinician might encounter in a clinic, higher pre-test probability of CTS in these settings lead to higher artificial estimates of diagnostic accuracy properties of the tools^{1,38}. Only three studies recruited their sample from a non-clinical population, where still the probability of having CTS was high since the inclusion criteria consisted of the workers with current hand symptoms^{30,32,39}. In this SR, to eliminate the effect of pre-test probability of CTS in the sample population on diagnostic accuracy measures, we extracted (or calculated) positive and negative likelihood ratios, as these values are independent of the prevalence of the condition.

In this SR, studies with solely asymptomatic (i.e. healthy) patients as their control groups were excluded. Most clinicians, specifically hand therapists, are often presented with clients with similar signs and symptoms of upper extremity but with different diagnosis and disorder. Therefore, the inclusion of the studies with normal control group does not replicate the clinical setting population of the target clinicians, thus decreases the applicability of this SR. Moreover, a case-control design of a study measuring the diagnostic accuracy of a tool, where the controls are

healthy individuals, results in erroneous estimates of inflated specificity and negative predictive values²⁶.

2.4.3 Limitations

Studies had different interpretation criteria, samples and different reference standards to make comparisons; this resulted in the heterogeneity of the data and precluded a meta-analysis. Three of the included diagnostic tests (Boston carpal tunnel questionnaire, Lo and Wainner clinical prediction rules) were only examined in one or two studies which limited our ability to make a decision regarding the diagnostic accuracy of these tests. Another possible limitation of this SR is we may have missed studies, due to the variations in terminology. Although the search strategy of this SR was developed in consultation with a professional health sciences librarian, we cannot be certain that all of the eligible studies were included.

2.5 CONCLUSION

This SR summarizes the diagnostic accuracy of clinical diagnostic scales, questionnaires, and hand diagrams/maps for CTS diagnosis. According to the studies included in this SR, more invasive diagnostic tools for CTS (i.e. NCS) might only be necessary when there is concerns regarding the certainty of clinical diagnoses. More high-quality papers are necessary to confirm these findings. There's also a great need for the papers which look at the clinical triangulation process compared to electrodiagnosis or nerve conduction studies.

Table 2.2 Characteristics of the studies assessing diagnostic Scales and Questionnaires for the diagnosis of CTS and the reference standards in each individual study

Study (Authors, year, study design, country)	Diagnostic tool	Population Characteristics (sample size, n of cases with CTS, age, gender, duration/severity of symptoms, pre-exam CTS probability)	Participants selection process and setting, inclusion and exclusion criteria, control group diagnosis	Index test methodology, criteria for positive testing and interpreting clinician	Reference standard test methodology, criteria for positive diagnosis and interpreting clinician	Risk of bias
Bland (2000) ¹⁵ , prospective cross-sectional, UK	Bland symptoms questionnaire	7768 consecutive subjects, 3710 TP, age range 10 to 98 y, 5,392 women, symptom duration 0-3 months: 5.6%, 3-6 months: 17.8%, 6-12 months: 18.0%, longer than 12 months: 46.1%	All patients with suspected CTS referred for nerve conduction studies, No exclusion criteria reported	A small selection of questions, all of which were arranged in multiple choice/tick box, performed by the participants, A cut-off probability of 0.5	NCS of median and ulnar orthodromic sensory conduction from finger to wrist and measures of the motor terminal latency to abductor pollicis brevis recorded on both hands, supplemented by either a sensory potential recorded at the wrist on ring finger stimulation, performed by a neurologist. Normal values were defined as those within 2.5 standard deviations of the mean	Unclear (3 domains)
Bland et al. (2011) ³⁷ , retrospective cross-	Combined Kamath and Stothard Questionnaire	5860 consecutive subjects, no more detail on patients' characteristics	Patients who came to medical attention with suspected CTS for the first time. Excluded those with previous surgery to either side or	The CTS-7 includes examination findings (Tinel's and/or Phalen's signs) and we aimed to study data that could	NCS were carried out on both hands of all patients according to AANEM standards	Unclear (1 domain)

sectional, UK	e and CTS-7 (only questionnaire segments)		recurrence after successful conservative treatment. Did not exclude patients with concomitant pathologies, such as diabetic polyneuropathy or ulnar neuropathy.	be collected from the patient without medical intervention.		
Bland et al. (2014) ¹⁶ , prospective cross-sectional, UK	Bland web-based questionnaire	2655 consecutive subjects, 67% F, mean age of 54.2 y, 1430 TP cases	Primary care physicians' referrals of suspected CTS patients. Excluded those who already had known CTS prior to visiting the website, those having tests for follow-up purposes or who had already had treatment for one hand and were returning for management of the second. No exclusions were made on the grounds of age, gender or coincident pathology.	Patients were asked to visit the website at http://www.carpal-tunnel.net prior to their appointment and to (takes 20–30 min) Cut off point of website score of 40% were used to diagnose CTS	NCS according to guidelines published by the AANEM The NCS results were graded using the Canterbury severity scale for CTS, which represents the changes in sensory and motor nerve conduction velocities and amplitudes as a numerical scale increasing in severity from 0 (no abnormality) to 6 (extremely severe CTS).	High
Bougea (2018) ¹² , prospective cross-sectional, Greece	Greek Version of the Boston Carpal Tunnel Questionnaire	90 consecutive subjects, age (y) 57.3 ± 13.8 SD, 75% F, CTS severity grade 1: 18.9%, grade 2: 6.7% grade 3: 42.2%, grades 4&5&6: 12.2%	Patients referred to the electrophysiology laboratory with symptoms consistent with CTS. Included: age 18 y; first-time visitors not previously diagnosed by the investigators; absence of severe intellectual disability or cognitive impairment. Excluded: polyneuropathy; systemic diseases potentially associated with polyneuropathy, diabetes mellitus, renal failure, hypothyroidism, or amyloidosis; other diseases that cause hand symptoms, such as cervical radiculopathy, or thoracic outlet syndrome; pregnancy	The overall FSS and SSS scores of the BCTQ were calculated. Cut off point: scores of 1.95 or greater.	EMG based on the AANEM guidelines. Used the Canterbury severity scale for CTS, which expresses the modifications of sensory and motor nerve conduction velocities and amplitudes as a numerical scale for the EM grading of severity from 0 (no abnormality) to 6 (extremely severe CTS)	Unclear (2 domains)

<p>Bridges et al. (2010)²⁰, prospective cross-sectional, UK</p>	<p>KSQ</p>	<p>211 consecutive subjects, mean age (y) 52.7 ± 14.0 SD, 57% F</p>	<p>patients who had been referred for electrophysiological testing with symptoms suggestive of CTS. Excluded patients with diabetes</p>	<p>All patients attending a hand clinic routinely fill in the KSQ, which consists of nine questions relating to possible symptoms of CTS, performed by a rheumatologist Cut-off point: scores of greater than 6 and below 3</p>	<p>NCS, performed by a single trained doctor who was also responsible for administering the questionnaire. Positive test if: onset motor latency to APB of >4:2 ms, peak sensory latency to index finger of >4:0 ms, a difference in onset motor latency between APB and ipsilateral ADM of >1:5 ms, a difference in motor latencies between both APBs of >1:0 ms, or a reduction of median sensory amplitude of >50% of either the ipsilateral ulnar sensory latency, or of the contralateral median nerve</p>	<p>High</p>
<p>Fowler et al. (2015)⁹, retrospective cross-sectional, UK</p>	<p>CTS-6</p>	<p>85 consecutive subjects, mean age 55 y (range 28 to 87), pre-exam CTS probability: 6%, 55 TP cases</p>	<p>A dataset of patients referred to EDS from an orthopedic hand surgery practice with a higher prevalence of CTS than that in the general population.</p>	<p>The CTS-6 score was calculated by a blinded examiner who was not involved in the US or NCS. A score of 12 points was considered a positive CTS-6 score</p>	<p>They used latent class analysis (Bayesian methods) as their reference standard and compared the scores obtained from CTS-6 to NCS and US. NCS was conducted according to AANEM guidelines. A distal motor latency of 4.2ms and/or a distal sensory latency of 3.2 ms were used as the cutoff for a positive diagnosis of CTS. The cross-sectional area of the median nerve was measured at the inlet to the carpal tunnel, using a 13-6 MHz linear array transducer (SonoSiteM-Turbo), by a blinded hand surgeon. A priori cutoff of 10 mm² was used as the cutoff for a positive ultrasound examination</p>	<p>Unclear (1 domain)</p>

Hems et al. (2009) ¹⁴ , prospective cross-sectional, UK	Bland's Questionnaire	152 consecutive subjects, 108 women, Duration of the symptoms: 125 more than 12 months, 20 between 6 and 12 months, and seven between three and six months.	All patients referred to the Hand Clinic with suspected CTS during the period of the study were asked to consent to participation in the study and to complete the questionnaire.	A questionnaire that has two parts, filled by both the participants and clinicians Cut-off point: score of greater than or equal to 7	NCS, they measured the latency of sensory conduction: positive if thumb to median nerve was 40.5 ms greater than thumb to radial/ Motor latency: positive if median nerve to abductor pollicis brevis (APB) > 4.1 ms	Low
Kamath and Stothard (2003) ²¹ , prospective cross-sectional, UK	Kamath and Stothard Questionnaire	58 final number of consecutive subjects with definite diagnosis of CTS, 67 women in the original population before exclusion criteria applied.	Patients referred with diagnosis of CTS to a hand clinic Included: definite diagnosis of CTS by a physician Excluded: a possible generalized neuropathy (such as those with diabetes mellitus); Renal transplant patients, pregnant patients	A questionnaire based on the based on the BCTQ, filled in by a hand surgeon. Cut-off point: score >5 on KSQ	CTR Positive criteria: symptom relief at 2 weeks after surgery	Unclear (1 domain)
Lo et al. (2009) ¹⁷ , prospective cross-sectional, Canada	Lo carpal tunnel prediction rule	278 consecutive subjects, mean age (y) 50 ± 12.7 SD, 149 TP, 58.8% F,	Subjects referred to the electrodiagnostic laboratory over a 1-year period with a clinical suspicion of CTS	The subject's point score was determined by a physiatrist based on the information and clinical findings obtained during the history and physical examination.	NCS by a blinded electrodiagnostic technologist, AANEM references. Positive criteria: a combination of a median to ulnar transcarpal latency difference of 0.4 ms and median transcarpal latency of 2.2 ms.	Low
Makanji et al. (2012) ¹⁰ , prospective cross-sectional, USA	CTS-6	98 consecutive subjects, mean age (y) 55 ± 15 SD, 62% women, CTS severity: Mild (n = 16); Moderate (n = 46); Severe (n = 16)	Adult patients in the practice of three hand surgeons that were prescribed electrophysiological testing were invited to participate Included: patients suspected with CTS Excluded: prior carpal tunnel release, injury to the wrist or hand, previous electrophysiological testing of the median nerve and pregnancy.	The instrument assigns varying weights to six symptoms and clinical manoeuvres and determines the probability of having CTS using a logistic regression equation. Cut-off point: 50% score	NCS & EMG, the median nerve was stimulated at the wrist and antidromic sensory action potentials were recorded 13 cm distally at the index finger for DSL studies. The median nerve motor action potential was recorded at the abductor pollicis brevis muscle and stimulated at the wrist 7 cm proximal to the electrodes for DML studies The presence of one or both of the following: DSL of 3.6 ms or greater	Unclear (3 domains)

					and/or DML of 4.4 ms or greater based on AANEM	
Naranjo et al. (2007) ¹³ , prospective cross-sectional, Spain	Boston Carpal Tunnel Questionnaire	68 consecutive subjects, 105 wrists (54% bilat), mean age (y) 47 ± 11 SD, 56 women, 80 TP wrists, severity: 13 mild; 30 moderates; 37 severe. Mean duration of symptoms: 21 months (8-36 IQR)	adult patients with suspected CTS referred to the outpatient Rheumatology clinic Included: burning pain or numbness aggravated by sustained positions and relief by shaking or moving the hands, sleep disruption by symptoms, and daily complaints over at least a three-month period Excluded: surgery, or traumatic injuries at the target wrist, hypothyroidism, acromegaly, polyneuropathy or radiculopathy, pregnancy, fibromyalgia, rheumatoid arthritis or crystal arthritis or had received injections, or presented ganglions, tenosynovitis or arthritis	The BCTQ has two components: hand function scale and hand sensitivity (sensory). Filled by a rheumatologist. Two different diagnostic accuracy measures were calculated for each component. Cut-off point: BCTQ >3	NCS, AANEM referenced, performed by two neurologists	Unclear (2 domains)
Wang (2018) ¹ , prospective cross-sectional, USA	CTS-6, KSQ, Lo Clinical prediction rule, Wainner clinical prediction rule	408 consecutive wrists of 250 subjects, 255 wrists with definite CTS, mean age (y) 52 ± 14 SD, 181 women	Patients were identified and recruited through an orthopedic hand surgery clinic Included: patients who returned to the office after being previously referred for electrodiagnostic testing for the assessment of CTS Excluded: patients younger than 18 years of age and the inability to comprehend English or give consent	Questionnaires were filled by a hand fellowship trained surgeon. Cut off points of 18 on CTS-6; 5 on the KSQ, 10 on Lo Q; 3 on Wainner clinical prediction rule	Clinical diagnosis (no further explanations)	Unclear (4 domains)

Bland Q: Bland Questionnaire, AANEM: American Association of Neuromuscular and Electrodiagnostic Medicine, CTR: carpal tunnel release surgery, NCS: nerve conduction studies, EMG: electromyography, US: ultrasound, TP: true positive, CTR: carpal tunnel release surgery, EDS: electrodiagnostic studies, U/E: upper extremity, IQR: inter quartile range, SD: standard deviation

Table 2.3 Characteristics of the studies assessing symptom diagrams/maps for the diagnosis of CTS and their reference standards in each individual study

Study (authors, year, design, country)	Diagnostic tool	Population Characteristics (sample size, n of cases with CTS, age, gender, duration/severity of symptoms, pre-exam CTS probability)	Participants selection process and setting, inclusion and exclusion criteria, control group diagnosis	Index test Methodology, criteria for positive testing and interpreting clinician	Reference standard test methodology, criteria for positive diagnosis and interpreting clinician	Risk of Bias
Ammer et al. (1993), prospective cross sectional, Austria	Katz HSD	101 consecutive subjects (147 wrists), mean age (y) 57.7 ± 15.8 SD, 68 women, 120 wrists with classic, probable, or possible CTS.	Patients suspected with CTS. Asymptomatic hands and patients with normal NCV were excluded from the analysis	Patients were asked to mark pain, tingling and numbness in the diagram	NCS, all tests were performed with a Disa Counterpoint or a Disa 2000 EMG system. Normal values were: DL of motor fibers at a distance of 5.5 cm= $2.994 \text{ ms} + 0.004 \times \text{age}$, SD= 0.392, and antidromic conduction velocity of sensory fibers (Vs)= $71.99 \text{ m/s} - 0.3 \times \text{age}$, SD= 4.86	High
Bonauto et al. (2008), prospective cross sectional, USA	Katz HSD	All subjects with current hand symptoms (253); All subjects with numbness, tingling or pain (179) Mean age (y) 39.5 ± 10.9 SD, 48% F	workers from 12 worksites in the manufacturing (electronics, automotive parts, windows, cabinets, medical and fitness equipment) and health care (hospitals excluding direct patient care and health research) sectors. Excluded: sudden shoulder injury, Part-time workers, temporary workers, workers in a mobile job,	Workers were asked to complete a body map describing the distribution of pain or discomfort, in the neck, shoulder, elbow/ forearm and hand/wrist if they had problems in the past year which either lasted a week or more or had	NCS, AANEM referenced, performed by Nerve conduction technicians. Positive if: at least one of the following findings: median motor latency 4.0 ms and/or median sensory latency 3.7 ms	Unclear (1 domain)

			such as a forklift driver, or with more than four job tasks	occurred at least 3 times. A classic/ probable/ possible HSD rating was considered a 'positive'		
Calfee et al. (2011), prospective cross sectional, USA	Katz HSD	221 consecutive subjects (216 with DSL analysis), mean age (y) 31.8 ± 10.6 SD, 71% M, 59 positive CTS according to Katz scores	CTS suspects workers with hand symptoms from 11 companies or organizations Included: symptoms of burning, pain, tingling, or numbness. Excluded: a history of CTS, peripheral neuropathy, current pregnancy, or inability to have nerve conduction testing	The instructions asked subjects to shade in the area of the problem but not to try to represent the type of their symptoms on the diagram. Scoring was performed according to the recommendations of Katz and Stirrat with modification, scores were dichotomized as positive ("classic" or "probable") and negative ("possible" or "unlikely"). The scoring of the diagrams was done by 2 physicians and 1 occupational therapist	NCS with an automated device (NC-Stat; NEUROMetrix, Inc, Waltham, MA). Positive if: a DSL > 3.5 ms, DML > 4.5 ms, or paired transcarpal median-ulnar sensory difference (MUD) of > 0.5 ms. Trans-carpal DSL measurements were recorded in the long finger	Unclear (4 domains)
Franzblau et al. (1994), prospective cross sectional, USA	Katz HSD	411 consecutive subjects, mean age (y) 35.7 ± 10.5 SD, 41.6% M, pre-exam CTS probability: 15%	At risk workers from four unrelated companies Included: certain jobs were selected on the basis of the frequency of repetitive hand movements ("low", "medium" and "high"), and all workers with at	Similar to the diagram and instructions used by Katz et al. ³³ Patients were instructed to shade in the distribution of numbness, tingling, burning or pain in the	NCS performed by physicians certified in EDS medicine/ median and ulnar sensory conduction studies in the wrists using surface electrodes and fixed distances (14 centimeters, antidromic stimulation) Positive if: a difference of at least 0.5 milliseconds between median and	Unclear (3 domains)

			least 6 months tenure in those jobs were invited to participate.	wrists, hands or fingers on the hand diagram.	ulnar sensory peak latencies in the same wrist	
Katz and Stirrat (1990) ¹⁹ , Retrospective, USA	Katz HSD	149 random subjects, 85 wrists with definite CTS, mean age (y) 45.6 ± 14 SD, 73% F	Patients with U/E paresthesia, Included: CTS diagnosis, based on: NCS; unequivocal response to cortico-steroid injection in the carpal tunnel; improvement after CTR. Excluded: patients with presumptive diagnoses that were not confirmed by this criteria, Diabetes, heavy ethanol use, hypothyroidism, RA, renal disease, ulnar entrapment, cartilaginous lesions, dorsal cutaneous nerve injury, C6-C7 radiculopathy, symptomatic hamate fracture	Patients were asked to shade the area of their discomfort on the HSD and indicate their quality of symptoms. CTS patients were categorized into four categories: classic, probable, possible, unlikely.	Clinical diagnosis, Diagnoses, comorbid conditions and demographic data were abstracted from patients' charts without knowledge of their Katz HSD ratings.	High
Katz et al. (1990a) ³⁴ , prospective cross sectional, USA	Katz HSD	110 consecutive subjects, 145 wrists, mean age (y) 45.6 ± 14.4, CTS severity: Classic: 18; probable: 16; possible: 17; unlikely: 2	Patients over 18 y referred to a Nerve conduction lab for evaluation of U/E discomfort Control group diagnosis: cervical radiculopathy, Ulnar Neuropathy, brachial plexopathy, polyneuropathy	Patients were asked to complete an HSD before the conduction of NCS. CTS patients were categorized into four categories: classic, probable, possible, unlikely.	NCS performed on a Disa 1500 or Teca 42 apparatus with skin temperature maintained at 34-37 °C. Positive if at least one of the following findings: motor latency > 4.0 ms; sensory latency > 3.7 ms; sensory velocity < 50 m/s	Low
Katz et al. (1990b) ³³ , prospective cross	Katz HSD	110 consecutive subjects, 165 wrists, 44 wrists with definite CTS, mean age (y) 45.6 ± 14.4 SD, 66.4 % F	Patients suspected with CTS over 18 y referred to a Nerve conduction lab for evaluation of U/E discomfort Control group diagnosis: Cervical radiculopathy, Ulnar neuropathy	Patients completed a self-administered hand pain diagram that depicted both hands with dorsal and palmar views. Patients were asked to	NCS, the protocol included bilateral median and ulnar sensory and motor testing and electromyographic recording from the abductor pollicis brevis on the most symptomatic hand. Testing was done with standard	Low

sectional, USA				mark areas on the diagram corresponding to the location of their symptoms and to indicate the quality of their discomfort. CTS patients were categorized into four categories: classic, probable, possible, unlikely.	techniques on a Disa 1500 (Copenhagen, Denmark) or Teca 42 (Pleasantville, New York) apparatus, with skin temperature maintained at 34° to 37° C. If patients had median motor latency greater than 4.0 ms, sensory latency greater than 3.7 ms, or sensory velocity less than 50 m/s. Performed by neurologist.	
O'Gradaigh and Merry (2000), prospective cross sectional, UK	Katz HSD	105 consecutive subjects	Suspicion of CTS by the refereeing clinician on any grounds. Excluded: previously treated for CTS or with recognized associated conditions	Patients outlined their symptomatic areas on the katz HSD. Those with classical or probable distributions were considered positive.	NCS, sensory amp < 10 micro V or motor latency > 3.7 ms	Unclear (3 domains)
Szabo et al. (1999), prospective cross sectional, USA	Katz HSD	100 consecutive subjects, 50 subjects (38 women, 87 wrists) definite CTS, 50 subjects (40 women, 90 hands) with other diagnoses of U/E, age range of CTS: 20-73 y, age range of non-CTS: 28-7, duration of symptoms: 2 months to 20 years, pre-exam CTS probability: 15%	Patients who were evaluated and treated at an institution for hand, wrist, and forearm problems. Included: a clinical history of numbness and tingling in the median nerve distribution and/or night pain relieved by shaking of the hand; results of physical examination, including sensibility and provocative examinations, consistent with CTS; and relief of symptoms after CTR. Control group diagnosis: epicondylitis, de Quervain's and other tendinosis, radiculopathy, and hand pain of unknown etiology	Subjects completed the hand diagram themselves; it was then scored blindly by one of the authors as classic, probable, possible, or unlikely for carpal tunnel syndrome according to the criteria described by Katz and Stirrat	NCS, bilateral median and ulnar motor and sensory nerve conduction testing were the electrodiagnostic parameters considered. Testing was done with standard techniques with the skin temperature maintained at 34°C to 37°C.	High

HSD: hand symptoms diagram, DL: distal latency, NCS: nerve conduction studies, SD: standard deviation, DSL: distal sensory latency, DML: distal motor latency, amp: amplitude, CTR: Carpal Tunnel Release, ms: milliseconds, AANEM: American Association of Neuromuscular and Electrodiagnostic Medicine, SD: standard deviation

Table 2.4 Diagnostic Accuracy of Scales and Questionnaires for CTS diagnosis

Study (Authors, year)	Examination tool	Sensitivity	Specificity	PPV	NPV	+LR	-LR
Bland (2000)	Bland Q	79.1	55.6	69*	67*	2.66*	0.56*
Bland et al. (2011)	Combined KSQ and CTS-7 [^]	95.9	50	NR	NR	1.92*	0.08*
Bland et al. (2014)	Bland web-based Q	78	68	NR	NR	2.43*	0.32*
Bougea (2018)	Greek Version of the BCTQ	75.5	68.3	NR	NR	2.38*	0.35*
Bridges et al. (2010)	KSQ	87 (80-94CI)	87 (80-93 CI)	NR	NR	6.70*	0.15*
Fowler et al. (2015)	CTS-6	95 (86-99CI)	91 (74-99 CI)	NR	NR	10.5	0.05
Hems et al. (2009)	Bland Q	82 (72-90CI)	67 (41-87CI)	91	48	2.48	0.26
Kamath and Stothard (2003)	KSQ	85	NR	90	NR	NR	NR
Lo et al. (2009)	Lo clinical prediction rule	76	68	NR	NR	2.37*	0.35*
Makanji et al. (2012)	CTS-6	87	60	89	55	2.17*	0.27*
Naranjo et al. (2007)	BCTQ functional Scale	35.1	62.5	NR	NR	0.94	1.04
	BCTQ hand sensitivity Scale	48.6	60	NR	NR	1.22	0.86
Wang (2018)	CTS-6	56 (50-62CI)	71 (62-79 CI)	83 (76-88CI)	40 (33-47 CI)	1.93*	0.62*
	KSQ	74 (68-79CI)	64 (54-72 CI)	83 (78-87CI)	50 (42-58 CI)	2.05*	0.41*
	Lo rule	66 (59-71CI)	56 (47-65 CI)	78 (72-83CI)	40 (33-48 CI)	1.50*	0.78*
	Wainner clinical prediction rule	70 (64-75CI)	64 (54-72 CI)	82 (77-87CI)	47 (39-55 CI)	1.94*	0.47*
PPV: Positive Predictive Value, NPV: Negative Predictive Value, +LR: Positive Likelihood Ratio, -LR: Negative Likelihood Ratio, Bland Q: Bland Questionnaire, KSQ: Kamath and Stothard questionnaire BCTQ: Boston Carpal Tunnel Questionnaire, CI: confidence Interval, ^ only questionnaire segments were included for the analysis in the original study, NR: Not Reported * values calculated by the authors of this study							

Table 2.5 Diagnostic Accuracy of the Symptom Diagrams/Maps for CTS diagnosis

Study (Authors, year)	Examination tool	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	-LR
Ammer et al. (1993) ²⁹	Katz HSD	92.6	50	62.5	88.2	1.85*	0.15*
Bonauto et al. (2008)	Katz HSD	61	58	52	67	1.42*	0.67*
Calfee et al. (2011)	Katz HSD	38 (28-50CI)	81 (73-87CI)	54 (41-67CI)	69 (61-76CI)	1.63*	0.76*
Franzblau et al. (1994)	Katz HSD	34	84	27	88	2.12*	0.78*
Katz and Stirrat (1990)	Katz HSD	80	90	NR	NR	8*	0.22*
Katz et al. (1990a) ³⁴	Katz HSD	96	73	58	91	3.55*	0.05*
Katz et al. (1990b) ³³	Katz HSD	61	71	59 (48-68CI)	73 (66-80CI)	2.10*	0.54*
O’Gradaigh and Merry (2000)	Katz HSD	92	40	92	14	1.53*	0.2*
Szabo et al. (1999)	Katz HSD	76 (62-89CI)	76 (52-77CI)	36	95	3.17*	0.32*
HSD: Hand Symptoms Diagram, PPV: Positive Predictive Value, NPV: Negative Predictive Value, +LR: Positive Likelihood Ratio, -LR: Negative Likelihood Ratio, CI: confidence interval, NR: Not Reported * values calculated by the authors of this study							

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2.7 Appendices

Appendix 2.A: Search strategies in Medline, CINAHL, and Embase

OID Medline Search Strategy:

- 1- Carpal Tunnel Syndrome/
- 2- Carpal Tunnel Syndrome.mp.
- 3- Carpal Tunnel Syndrome/ or Nerve Compression Syndromes/ or Median Neuropathy/
- 4- Carpal Tunnel Syndrome/di [Diagnosis]
- 5- Median Neuropathy/di [Diagnosis]
- 6- median nerve entrapment*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

- 7- compression neuropathy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 8- Nerve Compression Syndromes/
- 9- cts.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 10- syndrome, carpal tunnel.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 11- 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
- 12- diagnostic test*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 13- clinical test*.mp.
- 14- diagnostic accuracy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 15- "Sensitivity and Specificity"/

- 16- sensitivity.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 17- specificity.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 18- roc curve.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 19- 12 or 13 or 14 or 15 or 16 or 17 or 18
- 20- 11 and 19
- 21- ("Symptom diagram" or "hand diagram" or "Flick sign" or "Provocative Test*" or "Phalen's test" or "phalen test" or "wrist flexion test" or "wrist extension test" or "reverse Phalen test" or "carpal compression test" or "Durkan's test" or "Tinel's sign" or "Tourniquet test" or "Gilliat test" or "Sensory test*" or "Motor Test*" or "Touchor vibration threshold" or "Current perception threshold" or "Two-point discrimination Semmes-Weinstein Monofilament Test" or "Thenar weakness" or "Thumb Abduction Weakness" or "thenar atrophy" or "Abductor Pollicis Brevis Manual Muscle Testing" or "CTS-Relief Maneuver" or "CTS-RM" or "Pin Prick Sensory Deficit" or "ULNT Criterion C" or "upper limb neurodynamic test Tethered median nerve stress test" or "Luthy's sign" or "luthy sign" or "scratch collapse test" or "Pinwheel" or "CTS-6 evaluation tool" or "The Alderson-McGall hand function questionnaire" or "Hand elevation test" or "Katz and Stirrat hand diagram"

or "katz hand diagram" or "Purdue Pegboard Test" or "Levine's Self-Assessment Questionnaire" or "Dellon-modified Moberg pick-up test" or "Self-administered diagram" or "web-based questionnaire" "Kamath and Stothard questionnaire" or "Lo Carpal Tunnel Questionnaire" or "scratch-collapse test" or "hyperextension test" or "Flinn Performance Screening Tool" or "FPST").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

22- 20 and 21

OID EMBASE Search Strategy:

- 1- carpal tunnel syndrome.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 2- median neuropath*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 3- median nerve entrapment*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

- 4- compression neuropath*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 5- entrapment neuropath*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 6- carpal canal syndrome.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 7- carpal tunnel compression*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 8- "neuropathy, median".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 9- "syndrome,carpal tunnel".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 10- carpal tunnel syndrome/
- 11- 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
- 12- clinical test*.mp.
- 13- "sensitivity and specificity"/

14- receiver operating characteristic/

15- differential diagnosis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

16- "diagnostic test*".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

17- ("sensitivity" or "specificity").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

18- "ROC curve".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

19- diagnostic accuracy/ or diagnostic test accuracy study/ or differential diagnosis/ or physical examination/

20- 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

21- 11 and 20

22- ("Symptom diagram" or "hand diagram" or "Flick sign" or "Provocative Test*" or "Phalen's test" or "phalen test" or "wrist flexion test" or "wrist extension test" or "reverse Phalen test" or "carpal compression test" or "Durkan's test" or "Tinel's sign" or "Tourniquet test" or "Gilliat test" or "Sensory test*" or "Motor Test*" or "Touchor vibration threshold" or "Current perception threshold" or "Two-point discrimination Semmes-Weinstein

Monofilament Test" or "Thenar weakness" or "Thumb Abduction Weakness" or "thenar atrophy" or "Abductor Pollicis Brevis Manual Muscle Testing" or "CTS-Relief Maneuver" or "CTS-RM" or "Pin Prick Sensory Deficit" or "ULNT Criterion C" or "upper limb neurodynamic test Tethered median nerve stress test" or "Luthy's sign" or "luthy sign" or "scratch collapse test" or "Pinwheel" or "CTS-6 evaluation tool" or "The Alderson-McGall hand function questionnaire" or "Hand elevation test" or "Katz and Stirrat hand diagram" or "katz hand diagram" or "Purdue Pegboard Test" or "Levine's Self-Assessment Questionnaire" or "Dellon-modified Moberg pick-up test" or "Self-administered diagram" or "web-based questionnaire" or "scratch-collapse test" or "hyperextension test" or "Kamath and Stothard questionnaire" or "Lo Carpal Tunnel Questionnaire" or "Flinn Performance Screening Tool" or "FPST").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

23- 21 and 22

CINAHL search strategy:

- 1- (MH "Carpal Tunnel Syndrome")
- 2- "median neuropath*"
- 3- "median nerve entrapment*"
- 4- "compression neuropath*"

- 5- "entrapment neuropath*"
- 6- S1 OR S2 OR S3 OR S4 OR S5
- 7- "diagnosis or assessment"
- 8- "diagnosis"
- 9- "diagnostic"
- 10- (MH "Diagnosis") OR (MH "Diagnosis, Neurologic") OR (MH "Diagnosis, Musculoskeletal")
OR (MH "Exercise Test") OR (MH "Functional Assessment") OR (MH "Patient Assessment")
OR (MH "Patient History Taking") OR (MH "Physical Examination") OR (MH "Sensitivity and
Specificity")
- 11- (MH "Diagnosis, Musculoskeletal") OR (MH "Diagnosis, Neurologic") OR (MH "Functional
Assessment") OR (MH "Patient Assessment") OR (MH "Patient History Taking") OR (MH
"Physical Examination") OR (MH "Sensitivity and Specificity") OR (MH "Skin Tests")
- 12- (MH "Sensitivity and Specificity") OR "sensitivity and specificity" OR (MH "ROC Curve")
- 13- "sensitivity"
- 14- "specificity"
- 15- S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S 14
- 16- S6 AND S15
- 17- "Symptom diagram" or "hand diagram" or "Flick sign" or "Provocative Test*" or "Phalen's test"
or "phalen test" or "wrist flexion test" or "wrist extension test" or "reverse Phalen test" or "carpal
compression test" or "Durkan's test" or "Tinel's sign" or "Tourniquet test" or "Gilliat test" or
"Sensory test*" or "Motor Test*" or "Touch" or "vibration threshold" or "Current perception

threshold" or "Two-point discrimination" "Semmes-Weinstein Monofilament Test" or "Thenar weakness" or "Thumb Abduction Weakness" or "thenar atrophy" or "Abductor Pollicis Brevis Manual Muscle Testing" or "CTS-Relief Maneuver" or "CTS-RM" or "Pin Prick Sensory Deficit" or "ULNT Criterion C" or "upper limb neurodynamic test" "Tethered median nerve stress test" or "Luthy's sign" or "luthy sign" or "scratch collapse test" or "Pinwheel" or "CTS-6 evaluation tool" or "The Alderson-McGall hand function questionnaire" or "Hand elevation test" or "Katz and Stirrat hand diagram" or "katz hand diagram" or "Purdue Pegboard Test" or "Levine's Self-Assessment Questionnaire" or "Dellon-modified Moberg pick-up test" or "Self-administered diagram" or "web-based questionnaire" or "Kamath and Stothard questionnaire" or "Lo Carpal Tunnel Questionnaire" or "scratch-collapse test" or "hyperextension test" or "Flinn Performance Screening Tool" or "FPST"

18- S16 AND S17

Appendix 2.B Conflicts of interest for included studies

Study	Conflict of interest
Scales and Questionnaires	
Bland (2000)	No conflicts of interest statement
Bland et al. (2011)	No conflicts of interest statement
Bland et al. (2014)	No conflicts of interest
Bougea (2018)	No conflicts of interest
Bridges et al. (2010)	No conflicts of interest statement
Fowler et al. (2015)	There was no outside funding for this study.
Hems et al. (2009)	No conflicts of interest statement
Kamath and Stothard (2003)	No conflicts of interest
Lo (2009)	No conflicts of interest statement
Makanji et al. (2012)	No conflicts of interest
Naranjo et al. (2007)	No conflicts of interest statement
Wang (2018)	No benefits in any form have been received or will be received related directly or indirectly to the subject of this article.
Hand Symptom Diagrams/maps	
Ammer et al. (1993)	No conflicts of interest statement
Bonauto et al. (2008)	None declared
Calfee et al. (2011)	No benefits in any form have been received or will be received related directly or indirectly to the subject of this article.
Franzblau et al. (1994)	No conflicts of interest statement
Katz and Stirrat (1990)	No conflicts of interest statement
Katz et al. (1990a)	Grant Support: By NIH Grants AR36308 and AR07530 and the Kellogg Program for Training in Research in Clinical Effectiveness
Katz et al. (1990b)	No conflicts of interest statement
O’Gradaigh and Merry (2000)	No conflicts of interest statement
Szabo et al. (1999)	No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

**Chapter Three: Content validation of the Kamath and Stothard
questionnaire: a cognitive interviewing study**

Title: Content validation of the Kamath and Stothard questionnaire: a cognitive interviewing study

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Funding:

Joy MacDermid was supported by a Canadian Institutes of Health Research Chair in Gender, Work and Health and the Dr. James Roth Chair in Musculoskeletal Measurement and Knowledge Translation.

Declarations of interest: No benefits in any form have been received or will be received related directly or indirectly to the subject of this article.

3.0 Abstract

Study design: Cross-sectional cognitive interviewing study

Introduction: Accurate diagnosis of carpal tunnel syndrome (CTS) is essential for directing appropriate treatment; and for making decisions about work injury claims. The Kamath and Stothard questionnaire (KSQ) is a self-reported tool used for the diagnosis of CTS. Comprehensibility and comprehensiveness of this questionnaire is critical to diagnostic performance and need to be established.

Purpose of the study: To describe how potential respondents, clinicians and measurement researchers interpret KSQ questions, in order to identify and resolve potential sources of misclassification.

Methods: Hand therapists (n=4), measurement researchers (n=4), participants with CTS (n=5) and a control group (n=5), were interviewed using cognitive interviewing techniques (talk aloud, semi-structured interview probes). A content analysis was conducted on the verbatim transcribed interviews using a cognitive interview framework and classification.

Findings: Areas where questions were unclear to some participants were recorded and categorized into five themes: clarity and comprehension (52%), relativeness (38%), inadequate response definition (4%), perspective modifiers (4%), and reference point (2%). Respondents also identified several symptoms of CTS that are not covered by the KSQ that might be of diagnostic value, e.g. weakness and dropping items.

Discussion: The problematic questions identified in the study have been reported to have low specificity and negative predictive values in a previous quantitative study. The content validity

issues identified may explain poor performance. Recommendations were made to modify the wording of the KSQ and the potential addition of three new questions.

Conclusion: Future studies should determine whether the modified questionnaire can provide better diagnostic accuracy.

Key words: Carpal Tunnel Syndrome, diagnosis, Kamath and Stothard questionnaire, content validation, cognitive interviewing.

3.1 Introduction

Carpal Tunnel Syndrome (CTS) is a condition caused by the entrapment of the median nerve within the carpal canal, and constitutes the most common compression neuropathy¹. Signs and symptoms of CTS are predominantly represented by pain, numbness, tingling, and weakness of the wrist and hand area innervated by the median nerve (lateral 3.5 digits)^{1,2}. Accurate diagnosis of CTS is important for directing appropriate treatment, and decisions about work injury claims. Although several tools exist for the diagnosis of CTS, there is no overall consensus on the best choice of clinical measures that assess the existence and severity of CTS³. Recent clinical practice guidelines by the American Academy of Orthopedic Surgeons have suggested that multi-item diagnostic tools should be used in the diagnosis of CTS.³

The Kamath and Stothard questionnaire (KSQ) is a brief version of Levine's questionnaire⁴ for identification of CTS.⁵ (see Appendix 3.A for the KSQ). Kamath and Stothard stated they have developed this questionnaire based on the questions from the Levine et al⁴ CTS outcome measure; however, the questions and scoring are different so it is unclear how it was used. One study suggested that the KSQ has a high sensitivity (85%) and positive predictive value (90%) compared to nerve conduction studies⁵ in diagnosis of CTS. The KSQ consists of nine questions with yes/no/not applicable answers that are summed to generate a total score⁵. According to a study conducted by Bridges et al. in 2010, those scoring higher than six on the KSQ, do not need any further testing for the confirmation of CTS diagnosis⁶ (87% specificity). Despite these promising results, there has been a lack of validation and limited investigation on this diagnostic tool.

Cognitive interviewing (CI) is a method of evaluating how potential respondents interpret and calibrate responses to items on a scale, and can potentially identify sources of error in questionnaires⁷. This technique mainly focuses on interpreting the thought and decision making processes that are used by the respondents to answer the questions of a survey⁷. The four main elements of the thought processes for answering questions were defined by Tourangeau's model of response, and are as follows: comprehension, retrieval, judgment, and response⁸. Identification of errors in questionnaires and consequent item revision would lead to improved psychometric properties of any questionnaire⁷. CI is one of the methods to assess the content validity of a questionnaire⁹, as content validity considers the ability and adequacy of a questionnaire to measure the concept that is being tested⁹.

3.1.1 Purpose of the study

The primary aim of this study was to describe how persons experiencing hand symptoms and expert hand therapists or researchers understand and calibrate responses to the Kamath and Stothard Questionnaire for carpal tunnel syndrome diagnosis.

3.2 Methods

3.2.1 Study design and ethics

This is a cross-sectional cognitive interviewing study, approved by the Hamilton Integrated Research Ethics Board (HIREB) at Hamilton, ON, Canada (project #5543, appendix 3.B), and all participants provided informed consent (Appendix 3.C).

3.2.2 Sampling and participants

A purposeful sampling technique was administered to ensure that information-rich participants for the study were included^{10,11}. As a result of this maximum variation technique, included participants consisted of two groups as follow:

A) Experts group:

The experts' group included 1) Hand therapists who are the experts in this field and understand CTS (n=5), and 2) Graduate students (enrolled in either a master's or PhD of Rehabilitation Science at McMaster University) who had knowledge about questionnaire construction and could provide data about common errors such as confusing, misleading, and double-barreled questions (n=3).

B) Patients group:

The patients' group consisted of 1) people that had been diagnosed with CTS (by either electromyography or nerve conduction studies or clinical examination tests) (n=5). Patients with different stages of CTS (two mild, two moderate, and one with severe CTS) were recruited to ensure diversity of experiences and potential responses; and 2) people who had upper extremity (UE) signs and symptoms (i.e. pain and tingling) but did not have a diagnosis of CTS (n=5). This data was used to make comparisons with the data gathered from the CTS group, in keeping with the intended use of this tool for screening purposes.

3.2.3 Recruitment

A) Recruitment of the expert group:

Hand therapy clinicians, and graduate students with a known interest in a) diagnosis and measurement theory, or b) CTS were approached and asked to participate in this study through email or in person. In addition, recruitment emails were sent to local hand interest group clinicians (please refer to appendix 3.D) by one of the research team members (TP), with an invitation to participate in the study.

B) Recruitment of the patients' group

For recruitment of the patients, a multi-faceted strategy was administered as follows. 1) Clinicians with interests in hand rehabilitation were emailed and provided with explanations about study and a recruitment flyer (please refer to Appendix 3.E to see the attached study flyer). They were asked to refer patients (if interested in participation) with target diagnosis/signs and symptoms to the researchers. 2) Posters (please refer to Appendix 3.F) were put up in several buildings of the McMaster University's main campus; and 3) the recruitment flyer was also shared on a few local Facebook groups. Potential participants were asked to contact the research team.

3.2.4 Inclusion and exclusion criteria

All of the participants were required to speak and read English to be eligible to participate in this a study.

A) Experts group:

Clinician experts required 1) a degree in one of the following majors: occupational therapy (OT), physiotherapy (PT), and medicine (i.e. hand surgeon, orthopedic surgeon); and 2) at least two years of working experience. Eligible graduate students were enrolled in either the Master or

Ph.D. programs in Rehabilitation Science at McMaster University and had professional background education (PT or OT).

B) Patients group:

Patients were eligible to participate if they met one of the following criteria: a) mild, moderate or severe CTS diagnosed by electromyography, nerve conduction studies, or clinical examination tests; or b) neurologic, musculoskeletal or vascular manifestations of upper extremity symptoms (e.g. cervical radiculopathy, shoulder arthritis, etc.)

No exclusion was made based on age or gender in any of the groups, or on educational level in the patients' group. Exclusion criteria for the CTS group were persons with potentially confounding co-morbidities: any generalized neuropathy such as diabetes mellitus, renal transplant patients, rheumatoid arthritis, hypothyroidism, or connective tissue diseases.

3.2.5 Demographic data

Information regarding participants' age, gender, duration and severity of CTS symptoms (if applicable), or professional backgrounds (if applicable) was collected by the interviewer. All of the participants' documents that included identifying information such as the audio(s) and demographic data collection sheets were coded with a predetermined coding system to maintain the anonymity of the participants when using illustrative quotes. The coding of the experts' group was E1, E2, E3... and the patients' group codes in CTS and Non-CTS groups were PC1, PC2... and PNC1, PNC2..., respectively.

3.2.6 Cognitive interviewing procedure

A single, face-to-face session of cognitive interviewing was conducted with 13 of the participants: the remaining participants (n=5) were interviewed over the phone. The CI sessions lasted for 0.5-1 hour and were audio recorded and transcribed for analysis. All of the interviews were conducted by one interviewer (AD), an experienced physical therapist with training in CI methods.^{9,12} Two practice interviews with potential experts group participants were conducted before the beginning of the study, for a practice of the use of the semi-structured interview guide. These two interviews were not included in the analysis.

Two cognitive interviewing elements that were implemented in this study were: 1) ‘think-aloud’, meaning that the participants were instructed to ‘think-aloud’ while answering the questions; and 2) ‘verbal probing’, where the interviewer actively tried to collect detailed information by probing the participants’ responses. The interviewer asked the participants to read each question and express their initial understanding of the question. Afterwards, the ‘verbal probing’ technique was employed, using both pre-determined open-ended questions (Appendix 3.G), and additional probes specific to the participants’ responses.

At the end of the interviewing session, participants were asked to provide general feedback on the questionnaire, using questions such as *“Is there anything about your symptoms that you feel was not covered by these questions today?”*

3.2.7 Sample size and saturation

Data were analyzed after each interview and interviewing continued until a trend was identified and a data saturation point was reached. The data saturation point in this study was

established as a point where three consecutive interviews did not yield in any new findings¹³, which occurred with 18 participants enrolled.

3.2.8 Data analysis

Demographic data were entered into STATA 14¹⁴, to generate descriptive statistics of the personal characteristics of the respondents. A qualitative content analysis technique was used to interpret, analyze, and summarize the data from the CIs^{10,15}. Interviews were transcribed after each CI session and were imported into Microsoft Word (in an question-by-question format) for analysis, using a cross-case analytical approach^{10,15}. Common themes and issues were noted from each question and were categorized in the following codes: Clarity/Comprehension, Relevance, Inadequate Response definition, Reference Point, Perspective Modifiers. This coding system was developed by one of the authors of this study (JM)¹². No additional codes emerged during the process of transcribing and categorizing the sources of response error. The coding process was done by the first author (AD) and reviewed for accuracy by another one of the research team members (JM).

3.3 Findings

3.3.1 Participants

Eighteen voluntary participants contributed to this study. The expert group included eight participants with backgrounds in PT and OT, and a mean work experience of 11.6 years (SD=6.4). The patient group consisted of ten participants at different stages of CTS and different types of upper extremity diseases. The mean age of the participants was 35.2 years (SD= 9.9); and the mean

duration of CTS symptoms was 3.9 years (SD=3.3). Table 3.1 illustrates the detailed demographic information of the participants.

Table 3.2 Participants Demographic information

Variable	Mean ± SD	Range	Frequency (n)	Percentage (%)
Participants with or without CTS (n=10)				
Age (y)	35.2 ± 9.9	19- 48		
Duration of symptoms (y)	3.9 ± 3.3	0.5-12		
Severity of CTS			2 mild, 2 moderate, 1 severe	
Type of occupation (if applicable)				
Manual			5	55
Not manual			4	45
Gender				
Women			8	80
Men			2	20
Experts group (n=8)				
Work experience (y)	11.6 ± 6.4	4-20		
Profession				
Occupational therapy			2	25
Physiotherapy			6	75
Level of education				
B.Sc.			3	37
M.Sc.			2	25
Ph.D.			3	37
SD: standard deviation, y: years, CTS: carpal tunnel syndrome				

3.3.2 Problematic themes identified by cognitive interviewing

All of the participants expressed some interpretive dissonance when responding to the questions. Overall, the content analysis of the transcribed interviews revealed the participants indicated 80 significant sources of response error that were categorized into the following themes.

Table 3.2 demonstrates the errors identified by the cognitive interviews, sorted based on the themes and participant groupings.

-----Please insert Table. 3.2 around here-----

1) Clarity/Comprehension: this theme was the most common (52%), and raised when a word or the entire question was perceived as being vaguely worded, causing different interpretations of the same question or difficulties in understanding¹². Clarity issues are described relative to each question below.

The concept of *tingling* appeared to be problematic and misleading to five participants in both groups for question #2: Has tingling and numbness in your hand woken you during the night? An example of this dissonance is a participant who initially answered 'no' to this question and asked for clarification. When she was explained about the meaning of tingling, changed her answer to 'yes'. Another participant also stated, *"I do not have numbness, no, but tingling... sometimes at night, it burns, I do not know how I use the word "tingling", I cannot define this word"* -PNC3

Aside from the concept of *tingling* noted in the previous question, the word '*pronounced*' in the third question seemed to be difficult to interpret, with nearly half of all participants (n=8) identifying concerns, as illustrated by the following examples. *"I think the word 'pronounced' is not necessarily an easy word to understand. I think people would understand the word 'worse or more noticeable' easier than pronounced"* -ES3; and: *"What do you mean by the word pronounced here? I am not sure if I understood this question completely"* -PNC2

Question #4 had the highest occurrence of misinterpretations and difficulties in comprehension (n=10). The main problem was the phrase *'trick movements'*; and most of the participants (mainly in the clinicians' group) recommended to reword this phrase to *'change in posture'*. As an example: *"I do not know what the word trick movement means. I think this is a difficult question to answer. We use tricky movements to show off something like a magic trick, not like a regular movement"* -EO1

In addition to the phrase *'trick movements'*, 2 of the participants in the CTS group could not comprehend the meaning of *"going away from your hands"*: *"I have no idea what this is asking. Do I have any trick movements to make it go away or to start tingling? This is what I do not understand. Also, I do not believe it is a trick movement; it is just a movement"* -PC5

Although seemingly a straightforward question, three of the participants made a mistake about the anatomical location of their little fingers in the fifth question: *"my little finger is the third one, the one in the middle"* -PC4; and *"I think my little finger could be any of the fingers, other than my thumb. It was not easy for me to answer this question and I think there might be different opinions about little finger"* -PNC3

Five participants, including four experts and one patient, raised issues of clarity regarding the sixth question. One of the experts stated, *"The word 'presented' I do not think that is the right word to use... does it mean that it just happened, or did you feel it?"* -EP3 A participant in the non-CTS group also identified a lack of clarity around the included activities. *"I am not sure if I understood 'knitting' but steering the car and reading the newspaper part were easy to understand for me. Also, when I use my laptop, it makes me painful"* - PNC2

Two comprehension issues raised by 10 participants on question #9 were the words ‘helped’ and ‘splint’, as these did not appear to have a common interpretation. The participants in the expert group believed that rephrasing the question would make it more understandable and proposed alternate wording. *“I always ask that question, and I like it. However, you’ve got to define what is a splint; people ask me this all the time. Is it a brace, is it a glove? I think splint is usually considered to be custom-made and made at a hospital; versus a brace which you can pick up from a shelf. I think it is a valuable question by just modifying it to: have your symptoms improved with using support on your wrist?”* -EP3

2) Relevance: 38% of concerns raised were coded as this theme, defined as when people had difficulties relating the questions to their condition or individual lives ¹². The concepts of ‘day’ and ‘night’ in the first, second and third questions were mentioned 17 times by the participants across all of the groups (question #1: *has pain in the wrist woken you at night*). The participants mentioned that asking about specific times (day and night) would cause misinterpretation of the questions since not everybody sleeps at night (i.e. night shift workers, nurses, doctors); therefore, it narrows down the relevancy and applicability of the questionnaire.

“Using the term night in this question could be problematic... I was thinking about saying “has pain disrupted your resting time?” because some people sleep during the day, some sleep during the night, it depends. Alternatively, say when you are sleeping” -ES3

“If somebody is working throughout the night and sleeping during the day, we cannot ask them about days and nights. I usually tend to ask patients about their symptoms during sleep” -EP2

Another issue was raised on the activities (reading a newspaper, steering a car, and knitting) mentioned by the sixth question. Eleven participants stated that those activities are not very common anymore and not everybody tends to do them, including themselves.

"I do get tingling when I am biking, but I do not knit or read a newspaper. Moreover, I do not have numbness. I think other activities might be included in the list to make it more relevant to everyone" -EO2

"I do not read a newspaper, but I read books, and I have tingling when I hold it for too long... also, I do not knit maybe we can add some more activities to this question" -PC3 Further, when follow-up probes with two of the participants who answered no to this question during the interviews, it became evident that they answered no because they do not do any of these activities. *"no, as I do not read a newspaper, drive or knit"-PNC3*

The last relevancy issues mentioned by the participants was regarding question #7: do you have any neck pain? Although only two clinicians mentioned this, it seemed reasonable to the research team to discuss this issue and address it. The expert stated that: *"In my opinion, this question doesn't really signify the differential diagnosis of CTS... the other one about little finger was creating a differential from ulnar nerve dysfunctions. As a clinician I want to check for the double crush syndrome, to see if the numbness is coming from the neck or the wrist and rule out brachial plexus injuries and cervical referral pain. Neck pain is widespread, and everyone gets neck pain, so I believe having a neck pain does not necessarily mean that it is not CTS ..."* -EP3

3) Inadequate Response Definition: refers to when participants state that a question does not have enough response options for them to be able to accurately represent their sign and

symptoms¹². Overall, RP theme was mentioned three times by the experts (4%) and they believed that the question #4 could provide more response options to the respondents. Firstly, they recognized relieving maneuvers as a set of exercises, stretching, and wearing braces; *"also you might get other non-movement related things, that might alleviate pain as well. It might be helpful if you want to see what alleviates symptoms to CTS, to see if they are doing any non-movement related, like wearing a brace or not moving the hand at all"* -ES3. Secondly, the experts believed that the question must be asking *'tingling OR numbness'* instead of *'and'*, therefore providing more response options for the respondents.

4) Perspective Modifiers: represents when respondents of a questionnaire respond differently to one question, based on their life experience, and personal or environmental factors¹². Three participants (4%) of the expert group, proposed that the concepts of *'pain'* and *'severe'* in questions One and Eight, respectively, are not well-defined, and need to be more clearly stated.

"The concept of 'pain' is not clear, and it might confuse different people based on their perception of pain" -EP3

"The word 'severe' is not well-defined. Some people who might be experiencing tingling and numbness during pregnancy, but it might not be severe, or they do not see it as severe, and they would answer 'no' to this question" -EO1

"Definition of the word 'severe' must be better stated; it might mean different things to different people" - EO2

5) Reference Point: this theme is defined as when respondents have shifted their reference points and have difficulty calibrating their responses to a question¹². It was the least prevalent one occurred in this study and only two of the participants in the non-CTS category mentioned that their reference points have changed.

“And, I do not have tingling when I drive because I do not tend to drive long distances anymore or rest my arms in driving if it is more than 30 minutes” -PNC4 response to question #6

“No. I should not say no though because it helped at night, but it did not help me at work. Because I know I should have worn them at work, but it was too difficult, so I am not using them at work...” -PNC1 response to question #9

3.3.3 Participants’ opinion on content coverage

At the end of each interview session, the participants were asked to provide feedback on the content coverage of the Kamath and Stothard questionnaire. All of the participants stated that this tool was brief and comprehensive, addressing most of the areas that are important for the diagnosis of CTS (sensory symptoms and pain). The main area that was not adequately addressed according to the interviews (mentioned by nine participants) was related to functional limitations (i.e. weakness of the grip strength, loss of dexterity, and dropping items) and muscle wasting that occur with chronic and severe stages of CTS^{2,3,16}.

3.4 Discussion

According to the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN), content validation must appraise both the relevancy and the

comprehensiveness of a tool¹³. This cognitive interviewing study identified many issues that could lead to the misinterpretation and response errors to a CTS diagnostic questionnaire which would potentially reduce the content validity and diagnostic accuracy of this tool.

Our study suggested that improvements might be made to clarity and specificity of items which would potentially improve the diagnostic performance of a revised CTS diagnostic questionnaire. The first improvement suggested were based on potentially improving existing items (Table 2.3). Following is a question by question analysis of the questionnaire, along with the main themes that emerged for each question, as well as the rationale for the proposed modifications.

-----Please insert Table 2.3 around here-----

Q1: Has pain in the wrist woken you at night?

Due to the possibility of a prolonged poor posture of wrist (excessive flexion or extension during sleeping at night, the pain sensation is often considered to be nocturnal¹⁹; however, according to the results of the interviews of the present study, specifying the time of the sleep might cause a reduction in the generalizability and relevancy of the question. Many people tend to work at nights and asking about their sleeping at night might lead to confusion and misinterpretation of the question. The data from this study might justify the poor specificity (44%) and negative predictive values (34%) of the Edwards study; To address the issues raised on the clarity and relevancy of this question, our research team suggested modifying this question to: “*Do you wake up because of pain in your wrist?*”

Q2: Has tingling and numbness in your hand woken you during the night?

The feeling of pins and needles, with or without numbness and sleep disturbances are identified as the most common feature of those presenting with CTS^{2,3,20}. The theories regarding sleep disturbance are controversial, but one of the widely accepted ones is fluid retention or redistribution of body fluids while sleeping²¹ (or generally in the lying position). Lying posture together with the wrist flexion or extension increase the pressure in the carpal tunnel and on the median nerve, therefore exacerbating the tingling and numbness associated with CTS²¹. All of the participants of this study found question two as the most critical question to be asked for the diagnosis of CTS. To address the relevancy issues raised with asking about the *night*, we proposed modifying the question to: “Do you wake up because of tingling or numbness in your fingers?”

Q3: Has tingling and numbness in your hand been more pronounced first thing in the morning.

The theory behind the increase of non-painful disturbances and pins and needles sensations during sleep time has already been discussed in explanations of the first and second questions. This question has been proved to have moderate to strong positive and negative predictive values²². The word *presented* caused comprehension issues and made this question more difficult to understand. Also asking about *morning* makes this question less relevant to the large target group of people with CTS. To address these issues, the research team have proposed modifying this question to:” Do you have tingling or numbness in your fingers when you first wake up?”

Q4: Do you have any trick movements to make the tingling, numbness go from your hands?

The rationale behind including this question is another feature of CTS, relating to the alleviation of the symptoms of CTS with shaking, resting their hands when driving or performing manual activities, and hanging out of the side of the bed¹⁶. All of the participants CTS group of this study (n=5) stated that they have developed a form of relieving technique, which included mild exercises, stretching, shaking or immobility; whether it abated the symptoms immediately or not. The current iteration of this question implies that it is solely asking about an immediate improvement of symptoms by minimum activity and has a low negative predictive value (42%)²². This question could be more comprehensive to include other movements, and non-movement positions that relieve the symptoms of CTS; therefore, we modified it to: *“Do you have any quick movements or positions that relieve your tingling or numbness?”*

Q5: Do you have tingling and numbness in your little finger any time?

This question discusses the sensory distribution of the ulnar nerve, which is one of the main differentials of CTS^{2,21}. Classic CTS usually involves sensory deficits of the median nerve which are the first three and a half fingers (not the fifth digit). The clarity issue raised on this item was addressed by just adding a short explanation of the anatomical location of the little finger: *“Do you have numbness or tingling in your little (small/5th) finger?”*

Q6: Has tingling and numbness presented when you were reading a newspaper, steering a car or knitting?

This question is developed based on the exacerbation of the CTS signs and symptoms by holding the wrist in flexion or extension position¹⁹. The pressure within the carpal tunnel has been proved to increase with a deviation of the wrist from the neutral position and is directly associated with CTS²⁴. This item is the only question of the KSQ which is measuring the functional aspects associated with CTS. All of the activities mentioned in this question include sustained wrist flexion or extension; however, based on the finding of this study, they might not be necessarily relevant to all of the respondents. Therefore, we decided to modify it to: “*Do certain activities (for example, holding objects or repetitive finger movement) increase the numbness or tingling in your fingers?*”

Q7: Do you have any neck pain?

This question is aiming to exclude several differential diagnoses of CTS, including cervical neuropathy and brachialgia. Pressure at any point on the brachial plexus might lead to a sensation of tingling and numbness on the median nerve innervated area; therefore, it is mandatory to rule out other diagnoses which have similar manifestations as CTS. The question was formatted as: “*do you often have neck pain?*” to better correlate the occurrence of neck disorders with CTS.

Q8: If applicable has the tingling and numbness in your hand been severe during pregnancy?

Pregnancy is one of the most well-known risk factors for CTS. The prevalence of CTS among pregnant women has been reported to be 34% in a cohort of 639 participants²⁵. Increased blood pressure during pregnancy due to hormonal changes seems to increase the pressure in the carpal canal, leading to subsequent feelings of CTS signs and symptoms²⁵. This question was not relatable to any of the participants of the current study. Further analysis may calculate

psychometric properties of the KSQ, incorporating two different versions, with and without this question. Meanwhile, to tackle the RP issues raised about the concept of *severe* in this study, it was reworded to: “*Did you have numbness or tingling in your hands when you were pregnant? (If relevant)*”

Q9: Has it helped the tingling and numbness on wearing a splint on your wrist?

Immobilization of the wrist and maintaining it in a neutral position decreases the pressure in the carpal canal and is the basis of using a splint²⁴. Furthermore, systematic reviews have indicated that night splinting (orthoses) with the wrist in neutral position is effective²⁶. According to the findings of the present study, the word *splint* causes comprehension issues; therefore, we modified it to: “*Have your symptoms improved with using a wrist support (i.e. brace or splint)? (if relevant)*”

3.4.1 Recommendations on potential addition of questions to the Kamath and Stothard questionnaire

Kamath and Stothard questionnaire seem to be missing one important factor of the Levine’s questionnaire. A simple look at the KSQ, it is evident that most of the questions are biased towards examining sensory symptoms, i.e. pain, numbness, tingling⁵. Despite the frequent complaints of the weakness and functional limitations of the CTS patients, only one question (question 6) addresses this construct.

Given the KSQ questions with the most confusion in our cognitive interviews are those with the poorest diagnostic accuracy in previous studies¹⁸ suggests changes are needed. Further

important elements were identified that may have diagnostic value (Table 4). Although cognitive interviewing can guide proposed changes, future investigations on reliability, validity and diagnostic accuracy would be needed before any recommendations for use could be made. In total we suggested three new potential questions which are listed below. The usefulness of the incorporation of these recommended questions as well as the best order for them is pending further analysis.

1) *Is your numbness or tingling mainly in your thumb, index, and/or middle finger?* We recommend the addition of this question for a more specific approach to the measurement of the median nerve distribution area. It could also be substituted with the second question, asking about tingling and numbness sensation in hands.

2) *Do you drop small objects like coins or keys?* There is only one question asking about function on the KSQ, and as mentioned earlier, the function is one of the main constructs of the Levine's questionnaire¹⁷. The participants of our study recommended the incorporation of more questions on functional limitations and impairments.

3) *Do you have numbness or tingling in your toes?* One of the main differential diagnoses for CTS is peripheral neuropathy, i.e. diabetes. The prevalence of CTS in those having diabetic neuropathies is reported to be high (30%), with the pathophysiologic mechanisms being very complex and not yet fully understood². Adding a comparative body location might improve the specificity of this questionnaire.

Incorporation of a hand diagram with the KSQ is suggested to complement the screening questions with a visual map of the symptoms (Figure 1) since they provide complementary information. Katz and Stirrat's hand diagram is proved to have high diagnostic accuracy when

combined with other clinical examination tests¹⁹. The following is an instruction that make for a better flow of the questionnaire, followed by the modified version of the questionnaire (Table 3.4) and a hand symptoms diagram (Figure 3.1).

Instructions: Please answer the following questions as yes or no. We will ask about numbness which some people describe as having no feeling or dead feeling. We will also ask about tingling which some people call pins and needles or prickly feelings. Pick the answer about your hand has felt over the last month. Also, by shading the diagram below, please show where you have experienced numbness, tingling, burning or pain.

Table 3.4 Suggested modified questionnaire

1	Do you wake up because of pain in your wrist?	Yes	No
2	Do you wake up because of tingling or numbness in your fingers?	Yes	No
3	Do you have tingling or numbness in your fingers when you first wake up?	Yes	No
4	Is your numbness or tingling mainly in your thumb, index, and/or middle finger?	Yes	No
5	Do you have any quick movements or positions that relieve your tingling or numbness?	Yes	No
6	Do you have numbness or tingling in your little (small/5 th) finger?	Yes	No
7	Do certain activities (for example, holding objects or repetitive finger movement) increase the numbness or tingling in your fingers?	Yes	No
8	Do you drop small objects like coins or a cup?	Yes	No
9	Do you often have neck pain?	Yes	No
10	Did you have numbness or tingling in your hands when you were pregnant? (If relevant)	Yes	No Not relevant to me
11	Do you have numbness or tingling in your toes?	Yes	No
12	Have your symptoms improved with using wrist support (i.e. brace or splint)? (If relevant)	Yes	No Not relevant to me

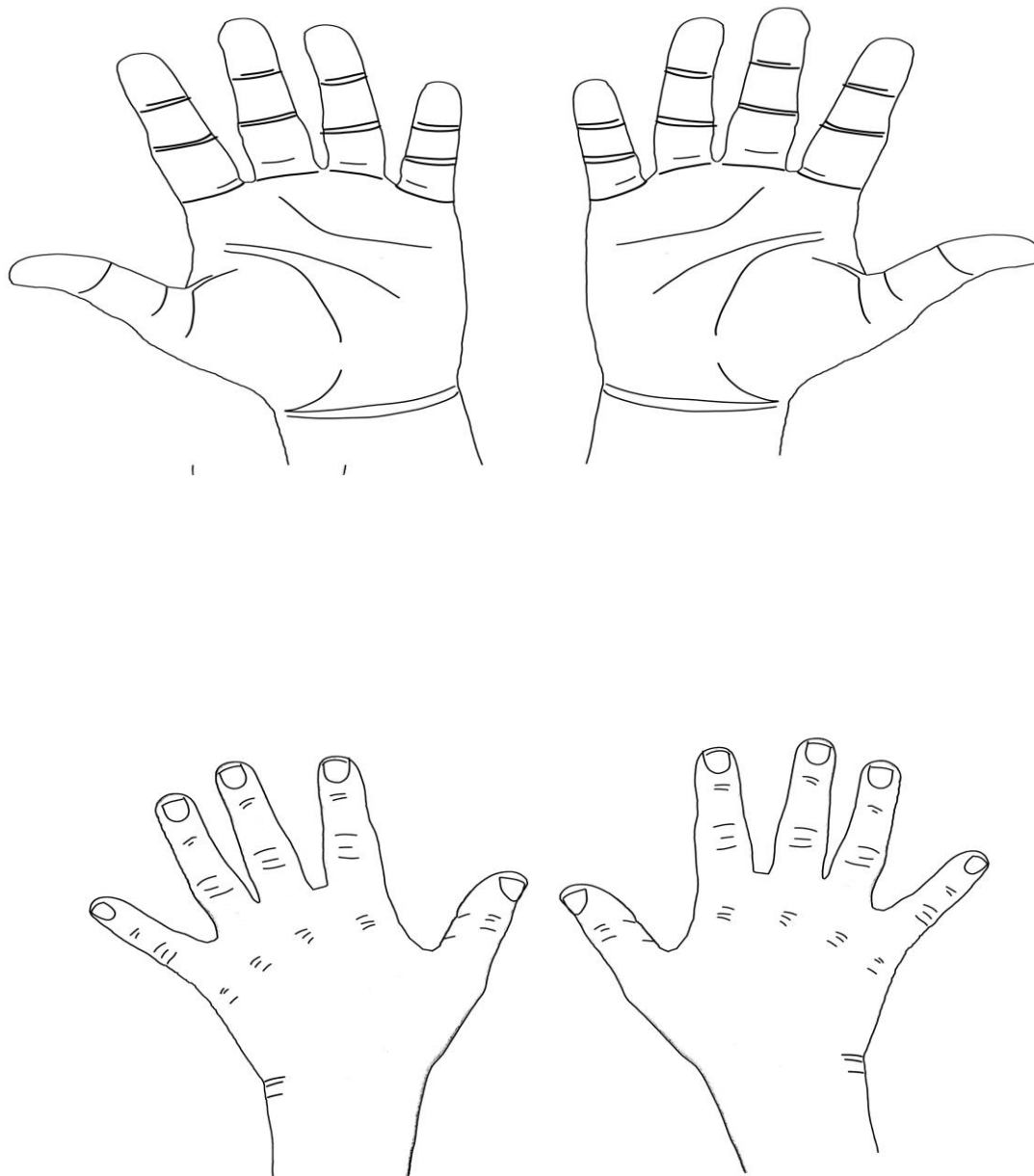


Figure 3.2 Katz and Stirrat's hand diagram²⁰

3.4.2 Limitations

One interviewer (AD) did the interviews, who consequently transcribed and did the analysis. This might have potentially introduced bias. To justify this shortcoming, the findings were discussed iteratively with a coauthor (JM) who reviewed and confirmed all of the coding for the content analysis. Further, all of the suggested modifications of the KSQ were discussed and established in two group meetings with at least two graduate students and including two of the research team members.

3.5 Conclusion

This CI study found multiple areas of uncertainty that could contribute to measurement error on a questionnaire designed for the diagnosis of CTS. Cognitive interviewing guided options for potential improvements in the wording of these questions. Testing of the diagnostic accuracy of the revised questions, and the potential addition of new questions is warranted given the limitation in validity of the currently existing tool.

3.6 References

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Table 3.2 Cross-item analysis summary of the response errors

Themes \ Questions	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total number of errors for each category across all of the questions
C		E:2 P:3	E:5 P:3	E:5 P:5	P:3	E:4 P:1			E:6 P:4	E:25 P:16 T:41
R	E:6 P:1	E:5 P:1	E:3 P:1			E:6 P:5	E:2	E:1		E:23 P:8 T:31
IR				E:3						E:3
RP						P:1			P:1	P:2
PM	E:1							E:2		E:3
Total number of errors for each question:	E:7 P:1	E:7 P:4	E:8 P:4	E:8 P:5	P:3	E:10 P:17	E:2	E:3	E:6 P:5	E:54 P:26 T:80
E: experts, P: patients, T: total, C: comprehension/clarity, R: relevance, IR: inadequate response definitions, RP: reference point, PM: perspective modifier										

Table 3.3 Modified versus original questions on Kamath and Stothard Questionnaire

Question #	Original questions	Modified questions
1	Has pain in the wrist woken you at night.	Do you wake up because of pain in your wrist?
2	Has tingling and numbness in your hand woken you during the night?	Do you wake up because of tingling or numbness in your fingers?
3	Has tingling and numbness in your hand been more pronounced first thing in the morning.	Do you have tingling or numbness in your fingers when you first wake up?
4	Do you have any trick movements to make the tingling, numbness go from your hands?	Do you have any quick movements or positions that relieve your tingling or numbness?
5	Do you have tingling and numbness in your little finger any time.	Do you have numbness or tingling in your little (small/5 th) finger?
6	Has tingling and numbness presented when you were reading a newspaper, steering a car or knitting.	Do certain activities (for example, holding objects or repetitive finger movement) increase the numbness or tingling in your fingers?
7	Do you have any neck pain?	Do you often have neck pain?
8	If applicable has the tingling and numbness in your hand been severe during pregnancy.	Did you have numbness or tingling in your hands when you were pregnant? (If relevant)
9	Has it helped the tingling and numbness on wearing a splint on your wrist.	Have your symptoms improved with using a wrist support (i.e. brace or splint)? (if relevant)

2.7 Appendices

Appendix 3.A KAMATH and STOTHARD Questionnaire¹

HISTORY (circle Yes/No number)

Has pain in the wrist woken you at night.

Yes 1 No 0

Has tingling and numbness in your hand woken you during the night.

Yes 1 No 0

Has tingling and numbness in your hand been more pronounced first thing in the morning.

Yes 1 No 0

Do you have any trick movements to make the tingling, numbness go from your hands.

Yes 1 No 0

Do you have tingling and numbness in your little finger any time.

Yes 0 No 3

Has tingling and numbness presented when you were reading a newspaper, steering a car or knitting.

Yes 1 No 0

Do you have any neck pain.

Yes _1 No 0

If applicable has the tingling and numbness in your hand been severe during pregnancy.

Yes 1 No _1 N/A 0

Has it helped the tingling and numbness on wearing a splint on your wrist.

Yes 2 No 0 N/A 0

Total

Reference: 1. Kamath V, Stothard J. A clinical questionnaire for the diagnosis of carpal tunnel syndrome. *J Hand Surg Am.* 2003;28 B(5):455-459. doi:10.1016/S0266-7681(03)00151-7

Appendix 3.C Information letter/consent forms

Principal Investigator:	Student Investigator:
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Purpose of the Study:

Carpal tunnel syndrome is a condition that causes pain and discomfort in the wrist area and the fingers. It is one of the most prevalent neural disorders of the upper limb. One of the safest, most convenient, and the most cost-effective ways to diagnose this condition is to use a simple and brief 9-items questionnaire called Kamath and Stothard questionnaire. Our study purpose is to find out whether or not this questionnaire is understandable by the patients and if they can easily respond to it.

Moreover, I am doing this research for my thesis to obtain a Master of Science degree in Rehabilitation Science. This is a line of research that I hope to continue in the future, however, we will not use your data for this project for any future related studies.

What will happen during the study?

You will be asked to: participate in a one-on-one interview with our researcher that will last approximately one hour. You would be asked questions on your signs and symptoms, and the time of the day or the activities during which you feel the most inconvenient or painful. There will be no sensitive questions and all of the questions are very straightforward and general. You can find the questions of the questionnaire attached to this form (Appendix A, Kamath and Stothard questionnaire). I will also ask you for some demographic/background information like your age and education. The interviews could be held over the phone, through skype or in person at McMaster University, Hamilton, Ontario.

Are there any risks to doing this study?

The risks involved in participating in this study are minimal. You may feel worried about your responses in the interviews or surveys (e.g., don't know how to answer or may be giving the "wrong" answer). They may also be concerned about a privacy breach. You do not need to answer questions that you do not want to answer or that make you feel uncomfortable. I describe below the steps I am taking to protect your privacy.

First of all, there is no right or wrong answers to the questions of this questionnaire. Secondly, nobody except me (student lead of this project and interviewer) would be able to recognize you, since we will be using a pseudonym, and your information will be de-identified in the analysis.

Are there any benefits to doing this study?

The research may not benefit you directly, however, we hope to learn more about the diagnosis of carpal tunnel syndrome (tingling, numbness and pain of the wrist area). I hope that what is learned as a result of this study will help us to better understand the criteria associated with the diagnosis of carpal tunnel syndrome. This could help many patients with hand and wrist area diseases to get diagnosed so much easier and faster.

Reimbursement:

Your participation in this study is appreciated and valued. You will be reimbursed by a gift card Worthing 20\$.

Confidentiality:

You are participating in this study confidentially. I will not use your name or any information that would allow you to be identified. No one but me will know whether you were in the study unless you choose to tell them. Nobody except me (student lead of this project and interviewer) would be able to recognize you, since we will be using a pseudonym, and your information will be de-identified in the analysis.

Paper files will be stored in a locked cabinet in a locked institutional office. Electronic files will be stored on a password-protected computer.

Data will be kept for 10 years, and after that paper files will be shredded confidentially.

Electronic files will be deleted using data wiping programs (in consultation with Computer Services Unit).

If the results of the study are published, your name will not be used and no information that discloses your identity will be released or published without your specific consent to the disclosure.

Participation and Withdrawal:

Your participation in this study is voluntary. It is your choice to be part of the study or not. If you decide to be part of the study, you can stop (withdraw), from the interview for whatever reason, even after signing the consent form or part-way through the study or up until *August 15, 2019*, when I expect to be submitting my thesis.

If you decide to withdraw, there will be no consequences to you. In cases of withdrawal, any data you have provided will be destroyed unless you indicate otherwise. If you do not want to answer some of the questions you do not have to do so, you can still be in the study. *If you volunteer to be in this study, you may withdraw at any time and this will in no way affect the quality of care you receive.*

Information about the Study Results:

I expect to have this study completed by approximately *March, 2019*. If you would like a brief summary of the results, please let me know how you would like it sent to you.

Questions about the Study: If you have questions or need more information about the study itself, please contact me at:

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Room 308, Institute of Applied Health sciences,
McMaster University

This study has been reviewed by the Hamilton Integrated Research Ethics Board (HiREB). The HiREB is responsible for ensuring that participants are informed of the risks associated with the research, and that participants are free to decide if participation is right for them. If you have any questions about your rights as a research participant, please call the Office of the Chair, HiREB, at 905.521.2100 x 42013.

Consent statement:

- I have read the information presented in the information letter about a study being conducted by Dr. Joy MacDermid and Armaghan Dabbagh of McMaster University.
- I have had the opportunity to ask questions about my involvement in this study and to receive additional details I requested.
- I understand that if I agree to participate in this study, I may withdraw from the study at any time.
- I have been given a copy of this form.
- I agree to participate in the study.

Name of Participant (Printed)

Signature

Date

Consent form explained in person by:

I have discussed this study in detail with the participant. I believe the participant understands what is involved in this study.

____Armaghan Dabbagh_____
Name and Role (Printed) Signature Date

1. I agree that the interview can be audio [video] recorded.

Yes

No

2. Yes, I would like to receive a summary of the study's results.

Please send them to me at this email address _____

Or to this mailing address: _____

No, I do not want to receive a summary of the study's results.

Appendix 3.D Recruitment e-mail

Hello,

My name is Armaghan Dabbagh, and I am pursuing a master's degree in Rehabilitation Science at McMaster University. At the moment, I am looking for 15 participants for my dissertation research, which is aiming to content validate of the “Kamath and Stothard Questionnaire” for diagnosis of Carpal Tunnel Syndrome. This study has been reviewed and obtained approval by the Hamilton Integrated Research Ethics Board under Project #5543.

The purpose of this e-mail is to ask for your collaboration in this study and to refer patients with the following characteristics to me:

- CTS patients' group: patients at different stages of CTS (mild, moderate, and severe), being confirmed by EMG, NCV, or clinical examination tests.
- Non-CTS patients' group: patients with neurologic, musculoskeletal and vascular manifestations of upper extremity like cervical radiculopathy, fibromyalgia, De Quervain's tenosynovitis, and tennis elbow.

There is no age or sex restriction for participation; however, all of the potential participants must be English-speakers. The patients must know that participation in this study is voluntary and their wish of not participating in the study does not affect their care with you. Please refer to the attached recruitment flyer for more information.

I would like to thank you in advance for your time and consideration. Potential participants can contact me directly at (647) - 916 - 1767 or through this e-mail address: dabbagha@mcmaster.ca. Additionally, if you require more information about this study, please feel free to contact me at the same telephone number or e-mail address.

Thank you in advance for your cooperation and support.

Sincerely,

Armaghan Dabbagh, BSc. PT, MSc. PT,
Master's candidate in Rehabilitation Science,
McMaster University, Hamilton, Ontario
Tel: 647) - 916 – 1767
dabbagha@mcmaster.ca

Appendix 3.E Recruitment flyer



**From a graduate student in Rehabilitation Science
McMaster University**

**Invitation to participate in a research study about content validation of a
questionnaire for Carpal Tunnel Syndrome diagnosis**

If you have had pain, tingling, and numbness in your hand(s), wrist(s), if you have been diagnosed with Carpal tunnel Syndrome, if you have neck, shoulder, elbow or wrist pain, then we would like to invite you to participate in our study.

At this interview:

You would be asked to: participate in a one-on-one interview with our researcher that will last approximately one hour. You would be asked questions on your signs and symptoms, and the time of the day or the activities during which you feel the most inconvenient or painful. The interview could be in person at McMaster University, or via skype and phone call.

In appreciation for your time, you will receive a 20\$ gift card.

**Please RSVP to:
Armaghan Dabbagh,
dabbagha@mcmaster.ca , or
(647) 916- 1767**

This study has been reviewed by the Hamilton Integrated Research Ethics Board under Project #5543.

Appendix 3.F Recruitment poster



**PARTICIPANTS NEEDED FOR
RESEARCH IN *Carpal Tunnel Syndrome diagnosis***

We are looking for volunteers to take part in a study of:

Content validation of Kamath and Stothard questionnaire: a cognitive interviewing study

If you have had pain, tingling, and numbness in your upper hand(s) and wrist(s), if you have been diagnosed with Carpal tunnel Syndrome, if you have neck, shoulder, elbow or wrist pain, then we would like to invite you to participate in our study.

You will be asked to: participate in a one-on-one interview with our researcher that will last approximately one hour. You would be asked questions on your signs and symptoms, and the time of the day or the activities during which you feel the most inconvenient or painful.

In appreciation for your time, you will receive a 20\$ gift card.

For more information about this study, or to volunteer, please contact:

*Armaghan Dabbagh
Institution of Applied Health Sciences
(647) 916 - 1767 or
Email: dabbagha@mcmaster.ca*

This study has been reviewed by the Hamilton Integrated Research Ethics Board under Project #5543.

**Call Armaghian Dabbagh
(647) 916 - 1767**

Or

Email:
dabbagha@mcmaster.ca

**Call Armaghian Dabbagh
(647) 916 - 1767**

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**Call Armaghian Dabbagh
(647) 916 - 1767**

Or

Email:
dabbagha@mcmaster.ca

Appendix 3.G Pre-planned probes

Practice question:

What job do you think you'd be terrible at?

Probes:

- How do you define “job”?
- How do you define “terrible”?

Question 1. Has pain in the wrist woken you at night.

- Say it in your own words please, or what do you think that item means, or what does that mean to you, or can you repeat the question I just asked in your own words?
- How did you arrive at that answer? Or, why did you say yes, no?
- Was that easy or hard to answer?
- I noticed that you hesitated - tell me what you were thinking
- What does the term “wrist” mean to you?
- What does the term “pain” mean to you? How do you describe (define) “pain”?
- What’s at night? How do you define night?
- Is there anything else besides pain that you think has an impact on your sleep?
- How do you remember that the pain has woken you at night?

Question 2. Has tingling and numbness in your hand woken you during the night.

- Say it in your own words please, or what do you think that item means, or what does that mean to you, or can you repeat the question I just asked in your own words?
- How did you arrive at that answer?
- Was that easy or hard to answer?
- I noticed that you hesitated - tell me what you were thinking
- What does the term “tingling” mean to you?
- What does the term “numbness” mean to you?

Question 3. Has tingling and numbness in your hand been more pronounced first thing in the morning.

- Say it in your own words please, or what do you think that item means, or what does that mean to you, or can you repeat the question I just asked in your own words?
- How did you arrive at that answer?
- Was that easy or hard to answer?
- I noticed that you hesitated - tell me what you were thinking
- What does the term “hand” mean to you? How do you describe (define) “hand”?
- What does the term “morning” mean to you? How do you describe (define) “morning”?

Question 4. Do you have any trick movements to make the tingling, numbness go from your hands.

- Say it in your own words please, or what do you think that item means, or what does that mean to you, or can you repeat the question I just asked in your own words?
- How did you arrive at that answer?
- Was that easy or hard to answer?
- I noticed that you hesitated - tell me what you were thinking

Question 5. Do you have tingling and numbness in your little finger any time.

- Say it in your own words please, or what do you think that item means, or what does that mean to you, or can you repeat the question I just asked in your own words?
- How did you arrive at that answer?
- Was that easy or hard to answer?
- I noticed that you hesitated - tell me what you were thinking
- What does the term “little finger” mean to you? How do you describe (define) “little finger”?

Question 6. Has tingling and numbness presented when you were reading a newspaper, steering a car or knitting.

- Say it in your own words please, or what do you think that item means, or what does that mean to you, or can you repeat the question I just asked in your own words?
- How did you arrive at that answer?
- Was that easy or hard to answer?
- I noticed that you hesitated - tell me what you were thinking

Question 7. Do you have any neck pain.

- Say it in your own words please, or what do you think that item means, or what does that mean to you, or can you repeat the question I just asked in your own words?
- How did you arrive at that answer?
- Was that easy or hard to answer?
- I noticed that you hesitated - tell me what you were thinking
- What does the term “neck” mean to you? How do you describe (define) “neck”?

Question 8. If applicable has the tingling and numbness in your hand been severe during pregnancy.

- Say it in your own words please, or what do you think that item means, or what does that mean to you, or can you repeat the question I just asked in your own words?
- How did you arrive at that answer?
- Was that easy or hard to answer?
- I noticed that you hesitated - tell me what you were thinking
- What does the term “severe” mean to you? How do you describe (define) “severe”?

Question 9. Has it helped the tingling and numbness on wearing a splint on your wrist.

- Say it in your own words please, or what do you think that item means, or what does that mean to you, or can you repeat the question I just asked in your own words?
- How did you arrive at that answer?
- Was that easy or hard to answer?
- I noticed that you hesitated - tell me what you were thinking
- What does the term “wrist” mean to you? How do you describe (define) “wrist”?

Additional questions:

Do you feel you had enough questions to describe your experience? Were there too many questions? Not enough?

Is there anything about your symptoms that you feel was not covered by these questions today?

Did you find any of the questions difficult to understand?

Reference:

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Chapter Four: Concluding Remarks and Future Directions

4.1. Overview of thesis manuscripts and their linkage

This dissertation aimed to address the lack of a comprehensive and up-to-date synthesis of the available diagnostic questionnaires and hand symptom diagrams/maps for CTS. Most of these tests were developed in the last two decades (Graham, Regehr, Naglie, & Wright, 2006; Kamath & Stothard, 2003; Lo, Finestone, & Gilbert, 2009; Wainner et al., 2005) and have not been fully addressed by any previous systematic review. To address this gap, we conducted a comprehensive systematic review of CTS diagnostic tests accuracy of these tests following the PRISMA guidelines for systematic reviews of diagnostic tests accuracy (Liberati et al., 2009). We conducted computer searches on MEDLINE, CINAHL, and Embase databases, and applied pre-specified inclusion and exclusion criteria in two phases to make sure that we included all eligible article (Dabbagh, Macdermid, Yong, Macedo, & Packham, 2018). We then appraised the articles using the QUADAS-2 tool (Whiting, Rutjes, Westwood, 2011) to rate the quality of evidence, risk of bias and any applicability concerns.

We extracted data on any reported diagnostic accuracy measurement, including sensitivity, specificity, positive and negative predictive values. We also extracted data on the population characteristics, test methodologies and different reference standards used in each article. To eliminate the effect of pre-test probability and prevalence of CTS on diagnostic properties, we tried to create 2 x 2 contingency tables to calculate positive and negative likelihood ratios where possible (Sedighi, 2013). Twenty-one articles met the eligibility criteria and were included in this review. Of these twenty-one articles, twelve studies evaluated the diagnostic accuracy of clinical questionnaires and scales, and nine assessed the diagnostic accuracy of hand symptom diagrams for CTS.

Through the results of this systematic review, we identified a CTS diagnostic tool called the Kamath and Stothard Questionnaire (Kamath & Stothard, 2003) had high diagnostic accuracy values reported in two studies (Bridges et al., 2010; Kamath & Stothard, 2003) and moderate diagnostic accuracy values in two other articles (Bland et al., 2011; Wang et al., 2018). Since this questionnaire has never been evaluated for content validity and because the item selection process was not well described, we hypothesized that these results could be due to the lack of a sufficient content validation. Therefore, we conducted a content validation study on the Kamath and Stothard questionnaire using a cognitive interview process (Willis, 2004). After receiving ethics approval, we started conducting interviews. Eighteen participants contributed to this study, including the following groups: 1) eight expert clinicians, hand therapists, and graduate students from McMaster University currently enrolled in either a Masters or Ph.D. program; 2) individuals the diagnosis of CTS (n=5) and other diagnoses of upper extremity (as a control to the subjects with CTS, n=5).

The qualitative data from this study were analyzed using a qualitative content analysis technique (Sandelowski, 2000). We used a framework developed by MacDermid (MacDermid, 2018) to inform the analysis process. Overall, 80 errors were identified by the interviews, and we categorized them into five themes: comprehension/clarity, relevance, inadequate response definition, reference point, and perspective modifiers.

Overall, these two manuscripts contribute to our body of knowledge about diagnostic tests for carpal tunnel syndrome. The two manuscripts complement each other, as the second study advances our understanding of the measurement properties to address a gap identified in the systematic review part of this thesis.

4.2 Lay summaries of thesis manuscripts

In this thesis, we conducted two studies to expand what we know about the best ways to diagnose carpal tunnel syndrome. The studies are as follows.

4.2.1 Lay summary of the first study: Diagnostic Accuracy of Scales, Questionnaires and Hand Symptom Diagrams for the Diagnosis of Carpal Tunnel Syndrome: A Systematic Review of Diagnostic Test Accuracy

Carpal tunnel syndrome is a condition that sets off problems in the wrists and hands. It can make your hands and fingers feel heavy. You might have burning pain or feel ‘pins and needles’ in your thumb and some of your fingers. It is important to figure out what is causing these feelings quickly. If these problems are found and treated quickly, you might not need to have surgery to make them go away.

We did a study to find out about all the tests that doctors and therapists can use if they think someone might have carpal tunnel syndrome. We were very interested in looking at what other doctors and researchers had already written about questionnaires and hand diagrams.

We collected all studies that were about these special tests for the diagnosis of carpal tunnel syndrome and combined them in one big study. These big studies are called systematic reviews. We searched four different electronic libraries for studies on the diagnosis of carpal tunnel syndrome, in August 2018. Two researchers each went through everything we found to make sure we included all of the important research.

For our systematic review, we found twenty-one studies. We carefully read every study and made notes about the different tests methods and what each study found. Then we used this

information to compare the different tests with each other, and decided which tests are the most helpful to diagnose carpal tunnel syndrome.

We learned that there were not many high-quality studies about carpal tunnel diagnosis. Based on what we found, the CTS-6 test can be a very useful test to diagnose carpal tunnel syndrome. This test uses six different tests together to be correct more often.

If we want to help doctors and therapists get better at testing for carpal tunnel syndrome, we need to keep doing research to find simple and accurate tests.

4.2.2 Lay summary of the second study: Content validation of the Kamath and Stothard questionnaire: a cognitive interviewing study

We did a study to see if a pencil and paper test used to help diagnose carpal tunnel syndrome asks questions that people with common hand problems can understand. This test is called the Kamath and Stothard questionnaire. The test has nine questions, and the answers can only be yes, no, or not applicable.

We talked to people who had hand problems, and researchers and therapists who might work with them. We asked everyone if they understood the questions. Sometimes we asked them to explain the questions to us. We also asked them how they decided whether to answer yes or no. They told us about any other signs and symptoms of carpal tunnel syndrome that they think are important but weren't on the test. We recorded everything they said, and then typed it out word-for-word so we could study what people said.

We realized that some of the questions on this test might be hard to understand. Other people pointed out there were important hand problems that were missing. We used this

information to suggest changes to the test to make it better for finding carpal tunnel syndrome.

Now we need to test this new version before it can be used by other health-care professionals.

4.3 List of Key Findings

This dissertation included two separate manuscripts, each with their own findings. Following is a brief explanation of the findings of each study.

The first study identified the following:

- Twenty-one articles met the inclusion criteria of the present systematic review.
- Twelve articles assessed the diagnostic accuracy of scales and questionnaires, which are as follows: Bland questionnaire (n=3), Kamath and Stothard questionnaire (n=3), CTS-6 (n=3), Boston carpal tunnel questionnaire (n=2), Wainner clinical prediction rule (n=1), Lo carpal tunnel prediction rule (n=2).
- Positive likelihood ratios (LRs) to diagnose or rule in CTS ranged from 0.94 for Boston carpal tunnel questionnaire to 10.5 for CTS-6 scale, and negative LR to exclude or rule out CTS ranged from 1.05 to 0.05 for the same diagnostic tools.
- Nine studies were identified on the diagnostic accuracy of Katz and Stirrat HSD.
- Positive and negative LR ranged from 1.42 to 8, and from 0.78 to 0.05, respectively. Only four studies had high methodologic quality.

The second paper identified the following:

- Questions with potential confusion for respondents in the current iteration of the Kamath and Stothard questionnaire.

- Some areas were not adequately addressed in this questionnaire, as stated by the respondents.
- These misclassifications were categorized into five themes, using a pre-established framework (MacDermid, 2018).

4.4 Limitations

As with any other research, the studies of this dissertation have their limitations. Although the limitations of each study have been described in the body of their individual papers, it is important to shed some light on the overall limitations of this dissertation.

Firstly, the revised Kamath and Stothard questionnaire proposed in this dissertation should not be considered ready for broad and independent clinical use for the diagnosis of CTS. This revised questionnaire has limited psychometric property data available. We did not test the revised version of the questionnaire that we proposed in the third chapter of this dissertation for its validity, reliability, and other psychometric properties.

A second key limitation is regarding the generalizability of the results of the cognitive interviews incorporated in this thesis since the enrolled population was mostly from Hamilton, an urban area in Southern Ontario.

Another limitation to consider is the revised Kamath and Stothard questionnaire relied on the English literature and feedback from English speaking participants and therapists. We tried to tackle this barrier by including participants who speak English as their second language. These participants provided valuable information regarding the comprehensibility of this tool.

Three other noteworthy limitations are regarding the systematic review study conducted in this dissertation. Firstly, the systematic review performed in this thesis, only included diagnostic questionnaires and hand symptom diagrams. We did not include the articles on other clinical tests for diagnosis of carpal tunnel syndrome, such as provocative and sensorimotor tests. Therefore, we cannot draw conclusions on the diagnostic accuracy of all of the clinical diagnostic tests that exist for CTS.

The number of included studies on each diagnostic tool (except for the hand symptom diagram/maps) was lacking leading to limited conclusions. Reporting bias is defined as the selective reporting of the information based on subjective preferences (Santaguida, Riley, & Matchar, 2012). We tried to eliminate the potential reporting bias by registering a protocol outlining the criteria for inclusion and exclusion of the articles, before finalizing the included studies (Dabbagh et al., 2018). We were also able to retrieve the full-text versions of all of the included papers, which in turn decreased the risk of reporting bias.

This systematic review could not overcome the spectrum bias of each individual study. Most of the included articles in our systematic review recruited their sample from contexts with a high prevalence of CTS, such as electrodiagnostic laboratories and hand clinics. Diagnostic tools might have different outcomes depending on the setting they are used (Santaguida et al., 2012); positive predictive values increase, and negative predictive values decrease in contexts with a high prevalence of any given condition (Sedighi, 2013). We tried to decrease the chance of spectrum bias by calculating and reporting likelihood ratios of the diagnostic tools, which are diagnostic measures independent from the prevalence of the diagnosis. We created 2 x 2 contingency tables to calculate likelihood ratios when they were not directly reported in the respective articles.

4.5 Impact of research and practice implications

The studies conducted through this dissertation have the potential to advance our knowledge in the field of rehabilitation sciences in several areas. Our findings will be important and beneficial to shape future studies in the area of CTS diagnosis. Together these two manuscripts advance the body of literature on the diagnostic accuracy tests for CTS.

The practice implications associated with this dissertation are to decrease the need to use aggressive, time-consuming and expensive approaches for CTS diagnosis. This body of research aims to inform the end-users including therapists, family physicians, general practitioners, plastic and orthopedic surgeons, to name a few, of other more conservative diagnostic methods. Multiple diagnostic questionnaires, scales, and hand symptom diagrams exist for CTS, with diverse interpretation methods across the studies. Our systematic review provides a resource for clinicians and hand therapists to refer to when they want to diagnose a suspected CTS case. Moreover, Evidence-Based Clinical Practice Guidelines are often informed by combining the results of individual systematic reviews. This systematic review aims to inform clinical practice guidelines, such as the American Physical Therapy Association guidelines and American Academy of Orthopedic Surgeons guideline for the Management of Carpal Tunnel Syndrome.

4.6 Knowledge Translation Recommendations

This study incorporated the conceptual framework developed by Graham et al. in 2006 (Graham et al., 2006), called the knowledge to action framework. This conceptual framework has been adopted by the Canadian Institutes of Health Research (CIHR). The knowledge to action framework has two components, being 1) knowledge creation and 2) action cycle (Graham et al., 2006). The knowledge creation funnel has three steps, and systematic reviews are at the knowledge synthesis level or second-generation knowledge (Graham et al., 2006). The present systematic review synthesized results based on the included individual articles using rigorous methodologies. Knowledge synthesis is an essential step in widespread implementation and creating knowledge tools and products (third-generation knowledge). Although more high-quality studies are needed to make a conclusive decision on the gold standard diagnostic tool for CTS, this systematic review can inform future clinical practice guidelines, and become more suitable to serve end-user informational needs.

The other study conducted in the body of this dissertation was a qualitative cognitive interviewing study which is not ready to be used by the end-users, yet. More studies assessing the reliability, validity and diagnostic properties of the revised Kamath and Stothard questionnaire needs to be conducted to move our findings forward to the next stage of knowledge translation cycle.

4.7 Future Research Directions

Future high methodological quality research on the clinical diagnostic tests to diagnose CTS are needed. Limitations of the included studies in our systematic review have been mentioned before, but more specific recommendations for improvement in methodology of the future studies are as follows: 1) random recruitment of the sample, 2) recruiting the sample from contexts other than hand clinics and electrodiagnostic laboratories to support generalizability, and 3) using better-defined reference standards for validation. Regarding the content validation study element of this thesis, there is a great need for future studies addressing the psychometric properties, responsiveness, and reliability of the revised proposed questionnaire. We recommend retesting the questionnaire, in different contexts, and with a hand symptom diagram (Katz & Stirrat, 1990), as a combined diagnostic tool for carpal tunnel syndrome.

4.8 Dissemination Plans

The structure of the studies will allow for the publication of both studies. Dissemination via journal publication with the target journals – Journal of Hand Therapy (intended for the qualitative cognitive interviewing study) and Journal of Orthopedic and Sports Physical Therapy (intended for the systematic review) is planned. Abstracts will be submitted to the Canadian Society of Hand Therapists and the British Association of Hand Therapists 2020 conferences. The target audience of these conferences are clinicians working in the field of hand and upper limb care, e.g. hand therapists, hand surgeons, orthopedic specialists.

4.9 References

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